THE PHARMACOLOGY
OF ANESTHETIC DRUGS



Fourth Edition

THE PHARMACOLOGY OF ANESTHETIC DRUGS

A SYLLABUS FOR STUDENTS AND CLINICIANS

By

JOHN ADRIANI M.D

Director Department of Anesthesiology
Charity Hospital, New Orleans Louisiana

Professor of Surgery
Tulane University School of Medicine

Clinical Professor of Surgery and Pharmacology
Louisiana State University School of Medicine

Professor of General Anesthesia
Loyola University School of Dentistry
New Orleans Louisiana



CHARLES C THOMAS PUBLISHER

SPRINGFIELD ILLINOIS U.S.A.

CHARLES C THOMAS PUBLISHER
BANNERSTONE HOUSE
301-327 EAST LAWRENCE AVENUE, SPRINGFIELD, ILLINOIS

Published simultaneously in the British Commonwealth of Nations by
BLACKWELL SCIENTIFIC PUBLICATIONS, LTD., OXFORD, ENGLAND

Published simultaneously in Canada by
THE RYERSON PRESS, TORONTO

First Edition, 1940
Second Edition, First Printing, 1941
Second Edition, Second Printing, 1942
Second Edition, Third Printing, 1946
Second Edition, Fourth Printing, 1947
Second Edition, Fifth Printing, 1950
Third Edition, First Printing, 1952
Third Edition, Second Printing, 1954
Third Edition, Third Printing, 1956
Fourth Edition, 1960

To

E A ROVENSTINE M.D

who with his emphasis upon the basic sciences
in the teaching of anesthesiology
prompted the preparation
of this syllabus



PREFACE TO THE FOURTH EDITION

Since World War II chemists and pharmacologists have intensified their interest in the relationship of chemical structure of drugs to pharmacologic activity This has led to the synthesis laboratory investigation and clinical trial of numerous new compounds Families of drugs having similar pharmacological responses have been developed from single parent derivatives by varying side chains and chemical groupings As a result, anesthesiologists have been besieged with numerous depressants stimulants antagonists and adjunctive drugs. Many of these have enjoyed only a brief span of existence and have already been discarded or supplanted by apparently more effective substitutes. Others appear to have earned a more permanent position and are enjoying widespread use

In addition to research on new products during the past decade, the older conventional drugs have been studied in more detail with more precise methods and refined apparatus In many cases data heretofore available only from animal studies have been obtained in man In this edition therefore it was necessary to both add data on new drugs and to bring up-to-date material on the well-established drugs used in clinical anesthesiology As heretofore, the emphasis has been placed upon the anesthesiologist s use and interest in these compounds

JOHN ADRIANI, M.D

New Orleans Louisiana

PREFACE TO THIRD EDITION

NEARLY A DECADE has passed since the first edition of this book was prepared. During this period anesthesiology has grown into a well-defined medical specialty. At the time of preparation of the original text, knowledge of certain aspects of anesthesiology was meagre.

Although much still remains to be learned concerning basic principles and fundamentals, considerable data has been added to our fund of knowledge over the ten year period. These advances in our knowledge have been in all aspects of anesthesiology. The greatest advances, however, have been in the pharmacological aspects of the science. Most of the recently acquired pharmacological data has been obtained in the operating room on surgical patients. Information not available from patients has been supplied by the laboratory. This newer clinical experience, coupled with the recently added laboratory investigations have made possible a re-evaluation of earlier reported subject matter. In many instances, modification of the existing subject matter has been necessary; in others the previous observations are still acceptable. As a result, certain gaps have appeared in the text which need to be filled if the book is to continue to serve the purposes for which it was intended and which it seems to have filled,as evidenced by five printings of the second edition. The author feels that before any further publication is made, the original text should be completely rewritten and brought as nearly up-to-date as possible.

The purpose and general plan remains the same. Likewise, there has been no departure from the original form save for the inclusion of tables of the less common drugs used only occasionally by the anesthesiologist. Some of the more pertinent subjects of clinical importance have been elaborated upon and presented in greater detail. This has resulted in a larger volume. The properties and actions of non narcotic drugs used in conjunction with anesthesia, such as curare, the central nervous system stimulants, and drugs acting upon the autonomic nervous system have also been summarized. In describing these substances emphasis has been placed on their relationship to anesthesiology.

The writer is indebted to Mr. William Branks Stewart of the Department of Visual Education, Louisiana State University School of Medicine, for the preparation of the diagrams used throughout the text.

JOHN ADRIANI, M.D.

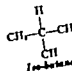
New Orleans, Louisiana

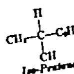
CONTENTS

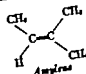
THE PHARMACOLOGY OF ANESTHETIC DRUGS



Branched Chain Derivatives—Both saturated and unsaturated derivatives have been tried and found to be limited in usefulness. *Amylene* has been used intravenously but possesses undesirable side actions.

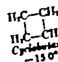

Iso-butane


Iso-Pentene


Amylene

Cyclic—Lower members of this series are useful. Methyl-substituted derivatives have been tried and found toxic. *Cyclopropane* and *cyclobutane* have been used clinically.


Cyclopropane −34.0°

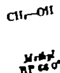

Cyclobutane −13.0°

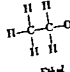

Methyl-cyclopropane 8.0°

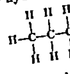
Lower molecular weight members are gases or volatile liquids which are poorly soluble in water but soluble in lipoids. Specific gravity is less than that of water. Narcotic potency increases as molecular weight increases. Narcotic potency increases as unsaturation increases (acetylene-ethylene-ethane). Hydrocarbons are chemically inert in vivo. Margin of safety varies but as a rule decreases as molecular weight increases. Some hydrocarbons cause deleterious effects upon cardiac tissues or induce undesirable neuro-muscular responses such as convulsions, twitchings, etc. Volatility and water solubility decrease as molecular weight increases.

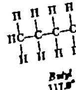
ALCOHOLS—The substitution of one hydrogen atom of a hydrocarbon by a hydroxyl (OH) group yields an alco Alcohols containing one hydroxyl group are known as monohydric alcohols, two dihydric, three trihydric, and so Alcohols are either aliphatic, alicyclic, aromatic or heterocyclic. Aliphatic alcohols produce hypnosis and ge anesthesia; aromatic and heterocyclic alcohols are important in local anesthesia (see local anesthetics). Alcohol classed as primary, secondary or tertiary depending upon the position of the hydroxyl group.

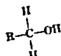
Primary Alcohols—Primary alcohols have two hydrogen atoms on the hydroxyl bearing carbon. *Ethyl alcohol* is the most important primary aliphatic alcohol with anesthetic activity.


Methyl BP 66.0°

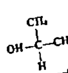

Ethyl 78.5

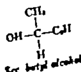

Propyl 97.0°

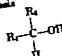

Butyl 117.0°



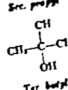
Secondary Alcohols—Secondary alcohols have one hydrogen and two radicals on the hydroxyl bearing carbon. No important secondary aliphatic alcohol is used for anesthesia or hypnosis.

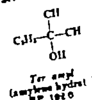

Sec. propyl


Sec butyl alcohol



Tertiary Alcohols—Tertiary alcohols have three radicals on the hydroxyl bearing atom. *Amylene hydrate* is the only currently employed drug in this group.


Ter butyl


Ter amyl (amylene hydrate) BP 102.0

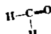
The substitution of the hydroxyl group for a hydrogen atom in an aliphatic hydrocarbon decreases its narcotic potency. Likewise water solubility increases, lipoid solubility decreases. The compound loses its inertness in vivo and becomes more reactive. Narcotic potency is decreased, and decreases still more with additional hydroxylation. Volatility and flammability are also decreased.

ALDEHYDES—Oxidation of primary alcohols yields compounds containing the aldehyde (CHO) group. The substitutio of a hydrogen atom of an alicyclic, aromatic and heterocyclic compound converts it into an aldehyde. Aldehyd polymerize to form metaldehydes and paraldehydes. Alcohol and aldehydes condense to form products known acetals. Paraldehydes and acetals depress the central nervous system.

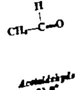
Aliphatic Aldehydes—Important aliphatic compounds are nervous system depressants. Acetaldehyde is the least toxic of this group, but is irritating and feeble in its action.

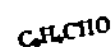
Alicyclic Aromatic and Heterocyclic Aldehydes—No important nervous system depressants exist in these groups.

Paraldehydes—Higher molecular weight paraldehydes have been studied but are toxic. Paraldehyde, the simplest member of the series, is useful as a sedative and hypnotic. Paraldehyde is derived from acetaldehyde.

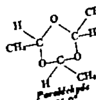



Formaldehyd BP −21.0°


Acetaldehyde 21.0°




Propionaldehyd 49.0°


Paraldehyde 121.0°

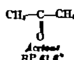
The conversion of an alcohol into an aldehyde causes an increase in irritating properties and a weakening of narcotic potency (ethyl alcohol is more useful and less irritating than acetaldehyde its corresponding aldehyde) Potency increases as molecular weight increases. Water solubility and volatility decrease as molecular weight increases.

Polymerization to paraldehydes forms an entirely new series of compounds distinctly unlike aldehydes. Paraldehydes are more potent than the aldehydes from which they are derived. They are also less soluble less volatile and less irritating Potency and toxicity increase as molecular weight increases. Volatility decreases as molecular weight increases. Halogenation of aldehydes enhances their potency (see halogenated derivatives)

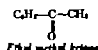
ACETALS—The interaction of alcohols with aldehydes produces acetals. Acetal is the most useful member of this group

KETONES—Oxidation of secondary alcohols yields ketones—compounds containing the carbonyl (C=O) group Ketones are of relatively little importance as central nervous system depressants. Halogenated ketones unlike the aldehydes are not useful as nervous system depressants.

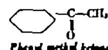
Phenyl methyl ketone or *hypnone* has been used as a hypnotic and sedative Potency of ketones increases as molecular weight increases.



Acetone
BP 61.8°



Ethyl methyl ketone



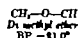
Phenyl methyl ketone

ACIDS—Organic acids are compounds containing the carboxyl (COOH) group The replacement of a hydrogen atom of a hydrocarbon by a carboxyl group nullifies its action as a nervous system depressant. The carboxylic acids therefore are of no importance as anesthetic agents.

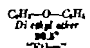
ESTERS—The interaction of an organic acid with an alcohol results in an ester Esters may be derived from aliphatic, alicyclic, aromatic and heterocyclic acids and alcohols. Esters derived from aliphatic alcohols and carboxylic acids are mild hypnotic and sedative substances. None are clinically important. Such esters are less potent than the alcohols from which they are derived. The majority of local anesthetic drugs are complex esters of aromatic or heterocylic acids and complex alcohols (see local anesthetic drugs)

ETHERS—Compounds formed by attaching two organic radicals to an oxygen atom are known as ethers. They may also be termed organic oxides. Ethers may be classed as aliphatic, alicyclic aromatic or heterocyclic. Aliphatic and alicyclic ethers are potent and useful for general anesthesia. Aromatic and heterocyclic ethers play no role in general anesthesia but appear in local anesthetics. Ethers may be symmetrical if both radicals attached to the carbon atom are similar or unsymmetrical if they are dissimilar Unsaturated linkages may appear on one or both radicals of ethers.

Saturated Aliphatic Ethers—*Di ethyl ether* is the most useful and potent of this group. Ethyl propyl ether has been used clinically also but is not generally accepted. Di methyl ether has been used clinically but is not satisfactory



Di methyl ether
BP −41.5°

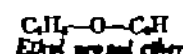


Di ethyl ether
34.5°
"Ether"

Unsaturated Aliphatic Ethers—*Di vinyl oxide* is the most important compound of this group. Higher molecular weight compounds are not satisfactory

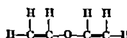


Methyl ethyl ether

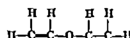


Ethyl propyl ether

Mixed Ethers—Various alicyclic and aliphatic ethers have been prepared and tried clinically None has yet attained any widespread clinical use Cyclopropyl methyl ether or cyprome, cyclopropyl ethyl ether or cypreth have been tried, but discarded.



Divinyl ether
BP 28.3°



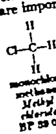
Ethyl vinyl ether

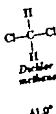
Aliphatic and alicyclic ethers are more volatile than the alcohols to which they are related or from which they are derived. They are miscible with lipoids and hydrocarbons, highly flammable and slightly soluble in water The presence of unsaturated linkages and the presence of the alicyclic radicals increases their potency

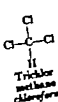
Low molecular weight ethers are very volatile irritating and require low concentrations for surgical anesthesia. Toxicity increases with increase in molecular weight. Halogenated ethers are not generally useful. Unsaturation causes an increase in secretory activity of ethers.

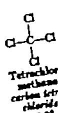
HALOGENATED DERIVATIVES—Compounds derived from chlorine fluorine and bromine are useful central ner system depressants. Iodine yields toxic or non-anesthetic derivatives. The most useful compounds are alip hydrocarbons, alcohols, and aldehydes. Alicyclic compounds are of no importance aromatic derivatives are toxic following aliphatic halogenated compounds are important

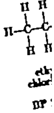
Halogenated Hydrocarbons (saturated)—Many derivatives of bromine and chlorine have been prepared which possess a depressant action on the nervous system. *Chloroform, fluothane* and *ethyl chloride* are currently used. The majority of derivatives in this group are administered by inhalation.



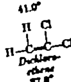


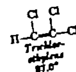


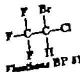




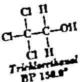
Halogenated Hydrocarbons (unsaturated)—*Trichlorethylene* is the only member of this group employed clinically for inhalation, other derivatives are irritating, toxic or not easily volatilized.

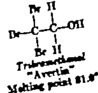


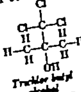




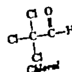
Halogenated Alcohols—*Trichlorethanol* and *tribromethanol* are potent hypnotics used for basal anesthesia. Drugs in this group are non-volatile and cannot be administered by inhalation. They are formed by reduction of aldehydes. Halogenation increases the potency of aliphatic alcohols.

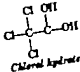


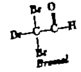




Halogenated Aldehydes—*Chloral* and *bromal* are used clinically These derivatives are more volatile than the corresponding halogenated alcohols. Halogenation diminishes irritating qualities and improves the potency of aliphatic aldehydes. Hydrates form when they interact with water Halogenated aldehydes, like the alcohols, are not sufficiently volatile to be used for inhalation.



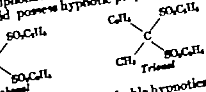


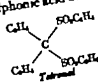


Halogenation enhances narcotic potency and causes a decrease in volatility of aliphatic substances. Inflammability decreases as the number of halogen atoms increases. Chlorinated derivatives are more volatile and less potent than brominated compounds. Many halogenated hydrocarbons are of limited usefulness because they are toxic to the heart and liver

SULPHONATED COMPOUNDS—Sulphur containing compounds are of little clinical importance with the exception of the thio-barbiturates (see barbiturates) and the sulphonated aliphatic compounds derived from sulphonic acid. The sulphone methanes, derived from ethyl sulphonic acid possess hypnotic properties. Aromatic sulphonic acid derivatives do not.

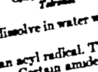
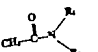
Sulphone Methanes—Three important compounds exist in this group *Sulphonal, trional,* and *tetronal.*





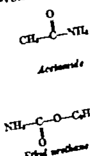
The sulphone methanes are little used clinically because they are feeble hypnotics. They dissolve in water with difficulty and possess cumulative properties.

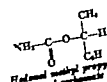
AMIDES—Amides may be considered as ammonia with one of its hydrogen atoms replaced by an acyl radical. They m also be considered as carboxylic acids with the hydroxyl group replaced by an amino group. Certain amides poss hypnotic and sedative actions. Amides are non-volatile drugs.

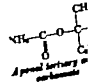



Substituted Aliphatic Amides—The amides have no depressant effects unless the hydrogen atoms are substituted by aliphatic aromatic and other groups. None of this group is employed clinically

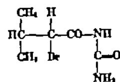
Urethanes—Carbamic acid, the monoamide of carbonic acid, forms esters with various aliphatic alcohols. This group of esters is known as *urethanes*. Ethyl carbamate or *ethyl urethane, hedonal,* and *aponal* have been used clinically Potency of urethanes increases as molecular weight increases Urethanes formed from primary alcohols are less potent than those formed from secondary those from secondary less potent than those from tertiary Ethyl urethane hedonal and aponal are important urethanes.



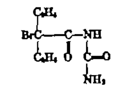




SUBSTITUTED UREAS—Urea the diamide of carbonic acid possesses no depressant action. Substitution of the hydrogens of the amino groups by alkyl, aromatic, aryl, and other radicals produces a large series of hypnotic derivatives.



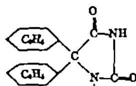
Bromural
brom-iso valeryl urea



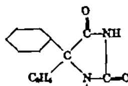
Carbromal
brom-diethyl acetyl urea

UREIDES—Urea reacts with carboxylic acids to form compounds known as ureides and water Monocarboxylic acids form open chain ureides dicarboxylic and other acids with two acidic groups form cyclic ureides. Two groups of cyclic ureides are important as central nervous system depressants—the hydantoins and the barbiturates.

Hydantoins—These are derived by condensation of glycocollic acid with urea. The five membered glycocollyl urea gives rise to two important anti-convulsants, dilantin and nirvanol, by substitution of the two hydrogens on the 5 position with aromatic and alkyl groups.



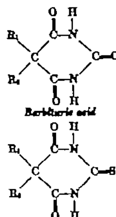
Diphenyl hydantoin
(dilantin)



Phenyl ethyl hydantoin
(nirvanol)

Barbiturates—These are derived by condensation of urea and malonic acid. The malonyl urea which forms is a six membered cyclic structure which gives rise to many hundred compounds if substitutions are made on the various atoms of the ring. Substitution of the two hydrogen atoms on the 5 position by alkyl, aromatic, alicyclic and other radicals yields some of the most useful sedative and hypnotic drugs used in clinical medicine.

Thiobarbiturates—Condensation of thiourea with malonic acid gives rise to a series of derivatives known as thiobarbiturates. These are similar to barbiturates with the exception that the oxygen atom is replaced by sulphur Pentothal is the most important member of this group.



Barbituric acid

MISCELLANEOUS SYNTHETIC HETEROCYCLIC AND AROMATIC ANALGESICS—Derivatives of piperidine (demerol) heptanone (methadon) ethylene diamine (anti-histamine drugs) aromatic amines (ephedrine), complex basic esters (atropine syntropan etc) derivatives of cyclopentenophenanthrene (various hormones) possess either general or local anesthetic action. The most important members of this group are methadon and demerol.

ALKALOIDS—Alkaloids are nitrogen containing substances elaborated by plants. The nitrogen usually in the form of a primary secondary or tertiary amine confers basic properties to the compounds. Alkaloids are usually aromatic, alicyclic or heterocyclic compounds. They are unique because minute amounts produce physiological activity They form salts with inorganic and organic acids. Alkaloids possess optical activity The alkaloids derived from opium are the only central nervous system depressants of clinical importance Alkaloids of the coca plant are useful local anesthetic drugs (cocaine) Numerous synthetic substances similar in properties and reactions to alkaloids have been prepared Many alkaloids formerly obtained from plants are now prepared synthetically

RELATION OF PHYSICAL AND CHEMICAL BEHAVIOR TO DEPRESSANT EFFECTS ON THE CELL

Depressant drugs exhibit a variety of chemical and physical properties in artificially prepared systems in vitro designed to simulate protoplasm. Similar behavior is believed to occur in the living cell.

Water Solubility—Volatile agents, as a rule, are poorly soluble. Useful non-volatile agents are soluble. All drugs must possess some water solubility to be carried to the cell. The majority of drugs are more soluble in blood than in water but parallelism exist between solubility in the two. Water solubility serves as an index of blood solubility.

Lipoid Solubility—Most drugs are highly soluble or miscible in oils and lipoids. A parallelism exist between solubility in lipoids and the quantity absorbed by nerve tissues since nerve cells are rich in lipoid substances.

Oil Water Ratio—Ratio of partition of the drug between equal volumes of oil and water at 37.5°C. Drugs possessing ratios of high magnitude are known as lipophilic agents. For the most part potency parallels increases in magnitude of this coefficient.

Colloids—Protoplasm is colloidal in nature. Colloidal properties are due to proteins. Proteins are coagulated by depressant agents. Colloid particles, because of their smallness and the fine division, present a large surface to the dispersion medium.

Adsorption—Many depressant drugs are adsorbed on surfaces of activated substances such as charcoal. The large surface possessed by particles in a colloidal solution favors adsorption.

Surface Tension—Many drugs decrease surface tension of water at room temperature. Similar decrease or decrease in interfacial tension may occur in protoplasm.

Viscosity—Viscosity of colloidal films is increased by man drugs. Changes in viscosity may cause decrease in pe meability of cell membrane.

Enzyme Activity—Many drugs decrease enzyme activ particularly those which facilitat oxygen utilizat such as oxidases and dehydrogenases.

EFFECTS OF DEPRESSANT DRUGS ON CELLS AND TISSUES

Lipoids—Lipophilic anesthetics are absorbed by cells rich in lipoid (nerve and adipose tissue). Depressant effect are more pronounced with drugs having high oil-water coefficients. Lipoids in the cells membrane may be altered by the drug and permeability thereby affected.

Stability—Most potent agents are inert or destroyed slowly in the cell. Ether, cyclopropane, ethylene, etc. are not altered by intracellular biochemical processes.

Intracellular Fluids—Water content of cell is decreased during depression induced by drugs. Fluids transudes outward. The reaction is reversible. Viscosity is increased. Intracellular pH is decreased.

Physical Phenomenon—Negative electrical polarity is decreased or reversed on nerve cells during narcosis. Electroencephalogram altered.

Cell Membrane—Cell permeability is decreased by depressant drugs. Change in permeability may be due to

1. Adsorption of drugs on constituents of the membrane.
2. Reduction in surface tension.
3. Alteration in constituents of the membrane.
4. Increase in viscosity of the membrane.

Colloids—An ultra microscopic coagulation or flocculation of protein may occur. Large concentrations of depressant drugs cause clouding of cytoplasm thought to be precipitation. Peptization or reversal occurs upon removal of the drug. (Claude Bernard-Bancroft.)

Metabolism—Carbohydrate metabolism of nervous tissues is depressed. Dehydrogenases are inhibited by many depressant drugs in vitro. Oxygen consumption is reduced.

Tolerance develops to depressant drugs. Repeated use causes habituation or psychic craving. Addiction (physical dependence) manifested physiological disturbances may result. This is due to inability of the cell to function unless drug is present.

Depressant drugs possess three characteristic features: (1) They depress all types of cells; (2) they have a special predilection for nervous tissue; (3) the action is reversible and the cells return to normal when the drug is removed from the cell.

THEORIES OF NARCOSIS

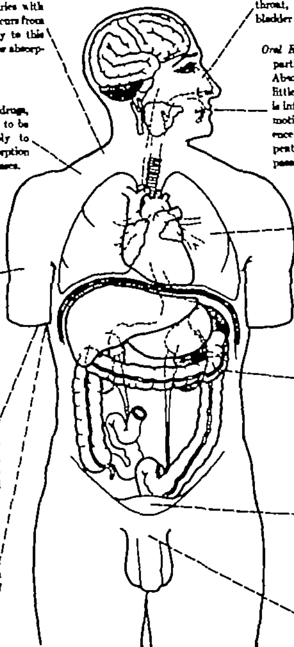
Narcosis is a reversible reduction of cell activity produced by physical or chemical agents. Physical agents such as cold electricity or pressure may also reduce cellular activity Chemical substances, both inorganic and organic, known as anesthetics, hypnotics and sedatives likewise reduce cellular activity No definite mechanism has been decided upon The following theories, based upon chemical, physicochemical or physical changes occurring in biological systems have been propounded

Basis of Theory	Year	Proposition	Proposer	Evidence	Objection
Lipoid solubility	1847	All fat solvents are narcotics. They cause narcosis by washing lipoids out of cells.	Bibra & Harless	Blood lipoid increases during anesthesia. Lipoid content of certain cells reduced.	Recovery occurs too rapidly to account for return of lipoid into the cell.
	1866 1893	Narcotic substances exert a direct reaction on cellular lipoids.	Hermann Richet	Aliphatic hypnotics dissolve in red blood cells because they are highly soluble in lipoids and lipoids are abundant in these cells.	Solubility in water not same as blood and lymph. Work done on olive oil and oils not similar to body fats. Applies to aliphatic compounds only and does not include or explain action of heterocyclic substances, alkaloids and *inorganic substances*. *Explains* mode of transport to nerve tissues but not its action in cell. Oil, water ratio not a true index of amount absorbed by tissues.
	1899 1901	Narcotic efficiency parallels *coefficient of partition* bet een oil and water Lipoids in cell and on cell membrane absorb drug because of this great affinity	Meyer Overton	Narcotic potency of aliphatic *compound increases as coefficient* of partition between oil and water increases.	
			K. Meyer	Concentration in moles per liter of drug which causes narcosis is constant and averages 0.03 moles/liter	
Surface affinity of drugs (Surface tension)	1904	Substances which lower surface tension of water pass more readily into the cell and cause narcosis by decreasing metabolism.	Traube Czapek	Parallelism exists between ability of drugs t lower surface tension of water and their narcotic potency	Experiments were done on air/water interfaces at room temperature Should be done on two liquid interfaces at body temperature Many exceptions-chloroform and ethyl alcohol.
Adsorption	1930	Drug becomes concentrated at the surface of the cell due to adsorption. Drug may thus alter permeability and alter metabolism.	King Also data by- Lillie Warburg and Hiller	Narcotic activity of certain drugs parallels amount of substance adsorbed at paraffin water interfaces. Certain drugs applied to surface of amebae cause depression of activity None if injected directly into cell.	Most of experiments have been done on artificial systems or in vitro Duplication of results in higher forms of life not successful.
Changes in permeability of cell membrane	1912	Permeability of cell membranes decreased by narcotic concentrations of aliphatic and other central nervous system depressants. Toxic concentrations increase permeability	Lillie Höber	Low concentrations of aliphatic substances added to aqueous media prevent swelling of nerve and muscle cells in hypertonic solutions.	Most experiments result of in vitro studies or from studies on structures of lower forms of life.
	1913		Winterstein	Lipoids concentrate at cell membrane because they lower surface tension. Drugs pass into lipoid in cell membrane, cytoplasm and decrease permeability and reduce metabolic activity	

Basis of Theory	Year	Proposition	Proposer	Evidence	Objection
Changes in colloid of cell ( ) Coagulation or flocculation of protein.	1867	Coagulation or flocculation of protein causes dehydration and reduction of metabolism.	Ranke	Noted clouding of muscle cells by chloroform which he thought was coagulation of protein.	Concentrations necessary to c coagulation experimentally gr than those encountered clinic Experiments done on unna systems in vitro or on ce lower forms of life
			Binz	Noted changes in transparency of cytoplasm of nerve cells after exposure t chloral and morphine	
	1875		Claude Bernard	Said narcosis due to reversible semi-coagulation of protein of cytoplasm of cell.	Narcosis does not always follow dehydration and fluid loss in cell.
	1882		Dubois	Noted shrinkage of cells due to loss of fluid following exposure to depressants.	
	1907		Höber	Noted shrinkage of cells due to water loss from cell following ex posure to depressants.	
	1931		Bancroft	Ultra microscopic reversible coagulation occurs which is visible with ultra microscope	
(b) Increase in viscosity	1930		Ebbeck	Drugs alter protein and increase viscosity of cytoplasm.	
(c) Combination with protein of cell.	1907	Narcotic combines with protein and other constituents of protoplasm. Drug becomes loosely adsorbed on colloids.	Moore & Roaf	Amount of chloroform in blood greater than physical laws of solubility allow	Amount of chloroform requir produce effect greater than necessary for narcosis.
Decrease in cellular oxidation	1880	Bivalent carbon atom which was thought to play role in cellular oxidation inhibited by narcotics.	Mathews-Brown	None	No experimental data.
		Depressant drugs interfere with tissue oxidation.	Bagloni	None	Anoxia and narcosis are not similar
(a) Oxygen deprivation.	1900	Narcotics cause oxygen deprivation which causes cell t be narcotized.	Verworn	Narcosis is accompanied by diminished oxidation.	Diminished oxidation is the result and not the cause of narcosis. Narcotics do not interfere with accessibility of oxygen to the cell.
(b) Narcotics inhibit oxidation.			Warburg	Activated charcoal adsorbs oxalic acid which is in turn oxidized. Anesthetics inhibit this oxidation.	Data obtained from in vitro experiments on a purely physical system.
( ) Inhibition of respiratory enzymes. (d) Suppression of formation of high energy phosphate bonds.	1934		Quastel, Wheatly and Janet	Oxygen consumption of brain slices in microrespirometer reduced because of decreased oxidation of glucose lactate and pyruvat	Are in vitro studies on excis tissues. Anesthetics mobilize ca bohydrates in tissues reduci availability and thereby decre ing oxidation. Suppression of o dation could be result of narc and not cause.
Electrical potentials of nervous tissue altered by narcotic drugs. Polarity reversed.	1936	Action potentials on brain tissue observed under narcotic drugs similar t those of normal sleep.	Burge, Derbyshire, Bremer and others	Reversal of polarity of cortex in relation t sciatic nerve occurs during narcosis	Describes the phenomenon of cosis rather than explains it.
Molecular volume	1937	Relates molecular volume determined by Vander Waal' constants	Wulf Featherstone		Many exceptions. Chl should be weaker than et cause molecule is smaller
Thermodynamic activity	1944	Interposition of narcotics in nonaqueous molecules in cellular phase cause changes which interfere with facilitation and ionic exchange	Ferguson, Mullins	Mathematical nd physicochemical in laboratory	

SECTION II. ADMINISTRATION ABSORPTION, AND ELIMINATION OF ANESTHETIC DRUGS

ROUTES OF ADMINISTRATION OF DRUGS



Subcutaneous Route—Useful for non-volatile water or oil soluble hypnotic and narcotic drugs. Not satisfactory for administration of irritating drugs which may cause sloughs. Rate of absorption varies with blood supply to the tissue. Slow absorption occurs from subcutaneous fat due to poor blood supply to this tissue. Oily solutions used for continuous slow absorption.

Intra-muscular Route—Useful for irritating drugs, drugs dissolved in oil or aqueous solutions to be rapidly absorbed. Excellent blood supply to muscle tissue favors rapid absorption. Absorption slow in shock or hypotension from other causes.

Intravenous Route—Useful for water soluble anesthetics, hypnotic and narcotic drugs. Factors which modify absorption by other routes are not present in this method. Desired blood concentration is promptly obtained. Has disadvantage of being non-controllable i e blood concentration cannot be varied or reduced in event of overdosage. Also drug may pass from blood and be stored in tissues causing cumulative action.

Intra-medullary Route—Useful when veins are not accessible. Sternum is used for adults, long bones for infants. Drug passes into venous circulation with almost same speed as if directly injected into the veins.

Intra-arterial Route—Not suitable. Spasm of artery and its tributaries may result in gangrene or other damage characteristic of ischemia.

Topical Route—No appreciable absorption occurs through the skin. Local anesthetic drugs pass through and anesthetize the mucous membranes of the nose throat, trachea, bronchi, urethra, vagina, rectum, bladder oesophagus and stomach.

Oral Route—Useful for non-volatile soluble drugs, particularly analgesics, hypnotics, and narcotics. Absorption is mostly from the small intestine little if any occurs from the stomach. Absorption is influenced by variable factors such as intestinal motility pH of intestinal contents, and the presence of other substances. Some drugs, such as pentothal and evipal, are rapidly destroyed on passage through the gastro-intestinal tract.

Pulmonary Route—Useful for gases and liquids which volatilize below 80°C. Gases and vapors gain access to blood by diffusion into the pulmonary capillaries through the alveolar membrane. Drug is carried to left heart and thence to the tissues.

Intraperitoneal Route—Useful for non-irritating non-volatile hypnotic and narcotic drugs. Large serous surface favors almost immediate absorption. Drug passes into lymphatics. Absorption greater in area around diaphragm. Used in animals. Danger of adhesions and infection precludes use in man.

Intrathecal Route—Useful for water soluble local anesthetic drugs to block nerve conduction. Drug slowly passes into venous circulation from spinal fluid.

Rectal Route—Useful for either volatile or non-volatile drugs. Vegetable or mineral oils are often used as vehicles for lipoid soluble drugs. Absorption proceeds almost entirely from the colon unless ileocecal valve is patent. Absorbed drugs pass through the liver which may cause modification or temporarily store them before passing into the systemic venous circulation.

SECTION II. ADMINISTRATION ABSORPTION AND ELIMINATION OF ANESTHETIC DRUGS

ROUTES OF ADMINISTRATION OF DRUGS

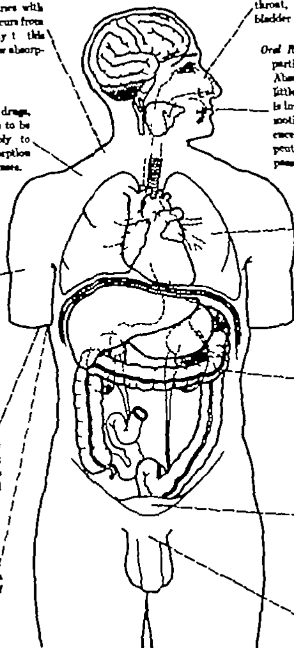
Subcutaneous Route—Useful for non-volatile water or oil soluble hypnotic and narcotic drugs. Not satisfactory for administration of irritating drugs which may cause sloughs. Rate of absorption varies with blood supply to the tissue. Slow absorption occurs from subcutaneous fat due to poor blood supply to this tissue. Only solutions used for continuous slow absorption.

Intra-muscular Route—Useful for irritating drugs, drugs dissolved in oil or aqueous solutions to be rapidly absorbed. Excellent blood supply to muscle tissue favors rapid absorption. Absorption slow in shock or hypotension from other causes.

Intravenous Route—Useful for water soluble anesthetics, hypnotic and narcotic drugs. Factors which modify absorption by other routes are not present in this method. Desired blood concentration is promptly obtained. Has disadvantage of being non-controllable i.e. blood concentration cannot be varied or reduced in event of overdosage. Also drug may pass from blood and be stored in tissues causing cumulative action.

Intra-medullary Route—Useful when veins are not accessible. Sternum is used for adults; long bones for infants. Drug passes into venous circulation with almost same speed as if directly injected into the veins.

Intra-arterial Route—Not suitable. Spasm of artery and its tributaries may result in gangrene or other damage characteristic of ischemia.



Topical Route—No appreciable absorption occurs through the skin. Local anesthetic drugs pass through and anesthetize the mucous membranes of the nose throat, trachea, bronchi, urethra, vagina, rectum, bladder oesophagus and stomach.

Oral Route—Useful for non-volatile soluble drugs, particularly analgesics, hypnotics, and narcotics. Absorption is mostly from the small intestine little if any occurs from the stomach. Absorption is influenced by variable factors such as intestinal motility pH of intestinal contents, and the presence of other substances. Some drugs, such as pentothal and evipal, are rapidly destroyed on passage through the gastro-intestinal tract.

Pulmonary Route—Useful for gases and liquids which volatilize below 40°C. Gases and vapors gain access to blood by diffusion into the pulmonary capillaries through the alveolar membrane. Drug is carried to left heart and thence to the tissues.

Intraperitoneal Route—Useful for non-irritating non-volatile hypnotic and narcotic drugs. Large serous surface favors almost immediate absorption. Drug passes into lymphatics. Absorption greater in area around diaphragm. Used in animals. Danger of adhesions and infection precludes use in man.

Intrathecal Route—Useful for water soluble local anesthetic drugs to block nerve conduction. Drug slowly passes into venous circulation from spinal fluid.

Rectal Route—Useful for either volatile or non-volatile drugs. Vegetable or mineral oils are often used as vehicles for lipoid soluble drugs. Absorption proceeds almost entirely from the colon unless ileocecal valve is patent. Absorbed drugs pass through the liver which may cause modification or temporarily store them before passing into the systemic venous circulation.

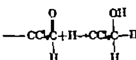
DETOXIFICATION OF DEPRESSANT DRUGS

Detoxification is the conversion of a *physiologically* active substance to one which is less active or inactive Although many tissues are capable of detoxifying drugs, the liver plays the dominant role in the process. Detoxification varies with the concentration of drug and the state of organism. Most drugs are detoxified by one or a combination of several of the following biochemical mechanisms

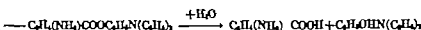
Oxidation—The drug is combined with oxygen and converted to various intermediate products or even completely oxidized to carbon dioxide and water Energy in the form of heat is liberated. Alcohols are detoxified in this manner Ethyl alcohol is converted to carbon dioxide and water Each gram liberates seven calories of heat.



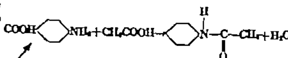
Reduction—This is the converse of oxidation. It is accomplished by the addition of hydrogen. Aldehydes may be detoxified in this manner Chloral, which is an aldehyde, is reduced to trichlorethanol, an alcohol.



Hydrolysis—Esters and other compounds capable of adding a hydrogen atom and a hydroxyl group are detoxified in this manner Procaine is hydrolyzed to an acid (para amino benzoic acid) and an alcohol (diethyl amino ethanol) The compound is split through the action of water to two or more compounds.



Conjugation—The drug is altered by combining it with another compound or radical to form new derivative which is inert or less active. Acids, amino acids or the methyl radical are used for combination. The conjugating substance is usually derived from some endogenous source:



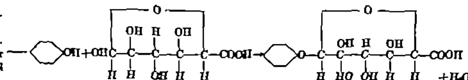
Acetic Acid—Used to add the acetyl group to amino compounds. Para amino benzoic acid, which is derived from procaine is changed to acetyl amino benzoic acid.

Cysteine—Used to detoxify halogenated compounds.

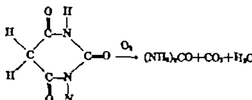
Sulphuric Acid—Used for conjugation with phenols. Phenol combines with it to form indican.

Glycine—Used for conjugation with aromatic acids.

Glycuronic Acid—Forms glucosides with alcohols or esters with acids. Tribromethanol, trichlorethanol and chloral are converted t glucoside type compound in this manner



Degradation—I certain cyclic compounds side chains are removed and the ring is disrupted so that no trace is found in the body Barbiturates are decomposed in this manner The exact mechanism is not known.



More than one mechanism may be employed in the detoxification and elimination of a drug. Ethyl alcohol is oxidized in the liver if concentrations are low Some is eliminated unchanged in exhalations and urine and some is detoxified if blood concentrations are high. Species variations are common. Amylene hydrate is conjugated with glycuronic acid in rats, and eliminated unchanged in man. Various enzymes, such as esterases oxidases, dehydrases, may assist in the detoxification. The blood contains an esterase which hydrolyzes procaine

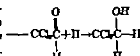
DETOXIFICATION OF DEPRESSANT DRUGS

Detoxification is the conversion of a *physiologically* active substance to one which is less active or inactive. Although many tissues are capable of detoxifying drugs, the liver plays the dominant role in the process. Detoxification varies with the concentration of drug and the state of organism. *Most drugs are detoxified by one or a combination of several of the following biochemical mechanisms*

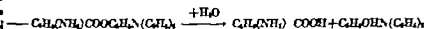
Oxidation—The drug is combined with oxygen and converted to various intermediate products or even completely oxidized to carbon dioxide and water. Energy in the form of heat is liberated. Alcohols are detoxified *in this manner.* Ethyl alcohol is converted to carbon dioxide and water. Each gram liberates seven calories of heat.



Reduction—This is the converse of oxidation. It is accomplished by the addition of hydrogen. Aldehydes may be detoxified in this manner. Chloral, which is an aldehyde, is reduced to trichlorethanol, an alcohol.

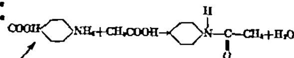


Hydrolysis—Esters and other compounds capable of adding a hydrogen atom and a hydroxyl group are detoxified in this manner. Procaine is hydrolyzed to an acid (para amino benzoic acid) and an alcohol (diethyl amino ethanol). The compound is split through the action of water to two or more compounds.



Conjugation—The drug is altered by combining it with another compound or radical to form a new derivative which is inert or less active. Acids, amino acids or the methyl radical are used for combination. The conjugating substance is usually derived from some endogenous source.

Acetic Acid—Used to add the acetyl group to amine compounds. Para amino benzoic acid, which is derived from procaine, is changed to acetyl amino benzoic acid.

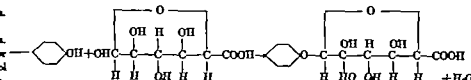


Cysteine—Used to detoxify halogenated compounds.

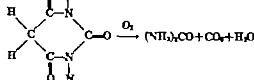
Sulphuric Acid—Used for conjugation with phenols. Phenol combines with it to form indican.

Glycine—Used for conjugation with aromatic acids.

Glycuronic Acid—Forms glucosides with alcohols or esters with acids. Tribromethanol, trichlorethanol and chloral are converted to a glucoside type compound in this manner.



Degradation—In certain cyclic compounds side chains are removed and the ring is disrupted so that no trace is found in the body. Barbiturates are decomposed in this manner. The exact mechanism is not known.



More than *one* mechanism may be employed in the detoxification and elimination of a drug. Ethyl alcohol is oxidized in the liver if concentrations are low. Some is eliminated unchanged in exhalations and urine and some is detoxified if blood concentrations are high. Species variations are common. Amylene hydrate is conjugated with glycuronic acid in rats, and eliminated unchanged in man. Various enzymes, such as *esterases, oxidases*, dehydrases, may assist in the detoxification. The blood contains an esterase which hydrolyzes procaine.

SECTION III. GENERAL SYSTEMIC EFFECTS

EFFECT OF CENTRAL NERVOUS SYSTEM DEPRESSANTS ON VARIOUS ORGANS

Brain—Depressed from above downward. Progressive depression results in paralysis of medullary centers. Respiratory center fails first usually

Salivary Glands—May be stimulated during induction and sec inhalation anesthetics—ether, chloroform, cyclopropane. Depre ing anesthesia. Most non-volatile substances depress from the o

Spinal Cord—Not affected until concentration causing medullary depression has been attained.

Trachea—Mucous glands stimulated by volatile Little affected by the gases and non-volatil

Lung Parenchyma—No histological effect ascribable to anesthetic concentrations of gaseous or volatile drugs. Respiration stimulated by some agents (ethers, halogenated hydrocarbons) by local action, no effect by others until medullary depression ensues (cyclopropane, barbiturates)

Thyroid Gland—Not significantly affected by most drugs.

Larynx—Locally irritated into spasm by drugs (ether, ethyl chloride). Centrally af others (cyclopropane, pentothal) not app affected by most agents.

Diaphragm—Usually last of respiratory muscles to be paralyzed.

Cilia—Activity depressed by most and non-volatile agents.

Metabolism—Depressed during anesthesia and hypnosis with most agents due to decreased activity

Heart—Myocardium ordinari depressed in anesthetic con trations except by certain h ated hydrocarbons (chlo ethyl chloride). Certain ag crease irritability of car tissue (cyclopropane, chlo trichlorethylene)

Lymphatics—Increased respiratory activity with some agents causes absorption from lymphatics of peritoneal cavity and diaphragm

Bronchi—Dilated by some chloroform, avertin. Constric others—cyclopropane pe No effect by others—nitrous ethylene

Peripheral Nerves—Action potentials unaltered until deeper planes of anesthesia are reached with most agents.

Autonomic Nervous System—Effects of sy stimulation with some agents ether, c form, vinethene are sympathetic. Cy pane and barbiturates are parasymp No effect by others (nitrous oxide, eth

Muscles—Potent inhalation anesthetics cause loss of tone from central depression. Mild agents (nitrous oxide and ethylene) do not affect tone appreciably. Paresis and paralysis of smaller muscles precedes that of larger muscles. Complete loss of muscle tone contributes to circulatory failure by diminishing venous return to heart (spinal anesthesia, curare)

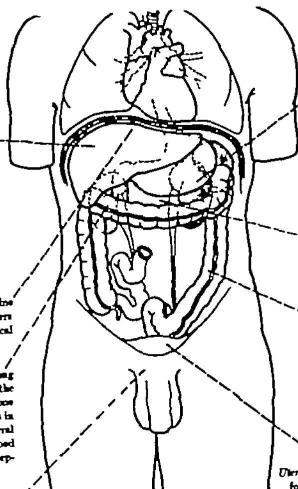
Blood—Hemoconcentration caused by most Hemodilution less common (barbiturates) volume reduced. Morphology of cells not Acid base balance disturbed by some agents chloroform) unchanged by others (cyclopr ethylene, nitrous oxide) Glucose increased mobilization of liver glycogen by some agents chloroform) Nitrogenous elements unchanged. ting mechanism not disturbed.

Liver—Ability of liver to excrete is most frequently studied function. Clearance of bromsulphalein is test most commonly used. Some cause no depression—cyclopropane, nitrous oxide ethylene, barbiturates. Others cause profound effect—ether chloroform. Anoxia superimposed on anesthesia causes profound changes. Local and spinal anesthesia no change. Bile flow not impaired by most agents. Chloroform and anoxia do impair. Glycogen stores depleted by sympathomimetic drugs—ether chloroform, anoxia. Urea formation not impaired. Ability to synthesize hippuric acid impaired by major agents. Prothrombin time not affected by any except chloroform.

Adrenal—Some cause depletion of epinephrine in the gland—ether chloroform. Others cause no effect. No notable effect on cortical hormones recognized.

Kidney—Urinary output suppressed during narcosis by most depressants. Probably the result of release of antidiuretic hormone from pituitary. Also affected by changes in blood pressure, renal blood flow, general fluid loss, (sweating, bleeding, etc.) blood electrolyte changes and decreased absorption from gastrointestinal tract.

Bladder—Atony with increased bladder volume follows depression of smooth muscle by some agents. Loss of sensation and desire to void further increases atony and contributes t post-operative urinary retention.



Spleen—Constricted by sympathomimetic drugs, anoxia and anesthetics which stimulate sympathomimetic action—ether and chloroform. Dilated during cyclopropane and spinal anesthesia. Blood flow need not be affected even though volume is decreased. Effect on pathological spleen with much fibrosis not pronounced. Changes in splenic volume reflected in blood and red cell volume. Enlarged when hemodilution occurs—barbiturates.

Pancreas—Inhibition of insulin action and production may occur—ether.

Gastrointestinal Tract—Potent anesthetics such as ether and chloroform inhibit activity absorption and secretion and reduce peristalsis. Milder drugs such as nitrous oxide ethylene have little or no effect. Certain drugs are spasmogenic—morphine, ether. Others are spasmolytic—demerol. Part of inhibiting action may be due to autonomic effects and part due to direct action on muscle.

Uterus—Major anesthetics such as ether and chloroform depress activity and motility. Depression progressive with depth of anesthesia. Mild anesthetics—nitrous oxide ethylene, vinyl ether—have little effect. Spasmogenic substances such as morphine inhibit motility and increase tone. Drugs pass through placenta.

VOLATILE VERSUS NON VOLATILE DRUGS

Central nervous system depressants are classed as volatile or non-volatile. Each type has certain physical and pharmacologic characteristics common to the group as a whole. Volatile liquids whose vapor pressures at room temperature are insufficient to produce adequate blood tensions for anesthesia when inhaled are classed with non-volatile drugs (alcohol).

General characteristics of volatile drugs are:

1. They are inert in the body and are eliminated unchanged.
2. Vapor pressures at room temperature are sufficient to produce narcosis when inhaled.
3. The tension in the brain necessary for anesthesia varies with the arterial tension. Arterial tensions are suitable indices of depth of anesthesia.
4. Are complete anesthetics. They possess analgesic properties and abolish transmission of impulses from the periphery to the higher centers (block lemnisco-thalamic pathways and reticular activating system).
5. They are poorly soluble in water (hydrophobic) and highly soluble in lipoids (lipophilic).
6. Variations in reflex activity (signs of Guedel) may be used as a guide to depth of anesthesia.
7. Provide controllable anesthesia. Tensions in the brain may be altered at will by varying the arterial tension by changing the inhaled concentration or by "washout" using artificial respiration.
8. The respiratory center is depressed before other vital centers. Respiratory depression or apnea may ensue before circulatory changes occur.
9. They may augment ventilation by local effects on pulmonary stretch and deflation receptors.
10. They cause reproductible changes in electroencephalographic pattern which vary with arterial tension of drug. Changes, therefore, serve as guide to depth of anesthesia.

Non-volatile drugs:

1. Do not completely interrupt pathways from periphery to the central receptors. Reflexes remain active.
2. Must be administered by routes other than inhalation. When administered parenterally ill-effects may ensue due to sudden perfusion of organ with a foreign substance.
3. Must be detoxified or are eliminated unchanged. This may require a long time.
4. Are not controllable. Must be administered in pre-determined doses. Once an estimated dose has been administered, it cannot be retrieved.
5. Delayed effects appear due to cumulation of breakdown products.
6. Blood plasma levels not an index of total concentration in body or brain.
7. May be bound to protein in plasma which inactivates them.
8. Depress all the vital centers simultaneously or the circulatory centers, at times, before respiratory.
9. Seldom completely abolish pharyngeal, tracheal and bronchial reflexes.
10. Nullify signs of anesthesia (Guedel).
11. May manifest untoward responses, such as intolerance, allergy.
12. May cause postoperative disorientation.
13. Are not analgesic. Are usually not adequate as sol anesthesia. Must be used in combination w drugs.
14. Do not stimulate local reflexes in mentation of ventilatory exchange.

GENERAL EFFECTS ON THE CENTRAL NERVOUS SYSTEM

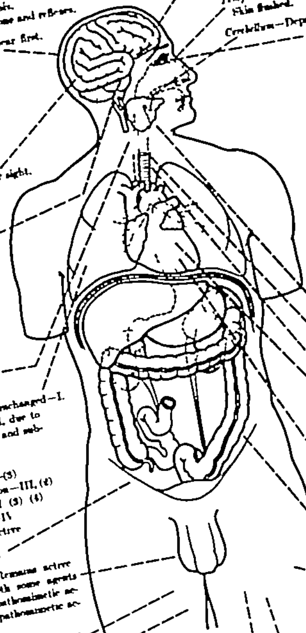
I FIRST STAGE—Analgesia—Due to depression of higher cortical centers.

II SECOND STAGE—Delirium or "excitement"—Cortic centers depressed.

III THIRD STAGE—Surgical—Automatic lower centers remain active but released from cortical control.
Spinal reflexes disappear
(1) First plane—Spinal reflexes disappear
(2) Second plane—Muscle tone decreased.
(3) Third plane—Complete intercostal paralysis.
(4) Fourth plane—Complete loss of muscle tone and reflexes.

IV FOURTH STAGE—Overdosage An irregular descendi involving in succession the cortex, basal ganglia, cerebellu and cord occurs. Signs are modified by premedication, an disable excess, leck, etc

Highest developed functions disappear first.



Cortex—Most highly developed functions disappear first.
Higher activities depressed—I
Motor areas slightly depressed—II
Sensory areas depressed—II
Inhibitory centers depressed—II.
Motor areas farther depressed—III.
Occipital lobe depressed—III
Frontal convolutions depressed—III

Cortical Areas—Olfactory area depressed—I
Sense of smell disappears before hearing or sight.
Auditory area not affected—I
Slightly depressed—II
Depressed—III, (1)

Medullary Centers—Respiratory center depressed—III.
Threshold to CO_2 elevated.
Does not respond to CO_2—IV
Respiratory movements cease before circulatory in most cases.
Cough center depressed—III, (1)
Vomiting center depressed—III, (1)
Medullary paralysis—III, (4) and IV

Vasomotor Center—Depressed III, IV
Unchanged I.

Respiration—Rate and movement unchanged—I.
Irregular depth may increase—II, due to release of inhibition of cortical and subcortical centers.
Regular respiration—III (1)
Lower intercostal lag—III (2)–(3)
Expiration longer than inspiration—III, (2)
Diaphragmatic respiration—III (3) (4)
Central respiratory paralysis—IV
Hering Breuer reflex remains active

Cord—Depressed after medulla.

Autonomic Nervous System—Remains active
Imbalance may occur with some agents giving semblance of sympathomimetic action (ether) or parasympathomimetic action (cyclopropane)

Motor Nerves—Action currents remain active I, II, III

Skeletal Muscles—Tone increased (due to red nucleus depression)—II
Small muscles relaxed—III, (1)
Large muscles relaxed—III, (2)
Complete relaxation—III (3), (4)
Diaphragm paralyzed—III (4)

Thalamus—Cortico-thalamic fibers interrupted—III
Basal ganglia depressed after the cortex.

Temperature Regulating Center—Depresse
Skin flushed.

Cerebellum—Depressed after the basal ganglia.

Eyes—Sight disappears before hearing—II
Pupillary reaction to light unchanged—I
Eyeball movement unchanged—I.
Pupil dilated, movements and reflexes unchanged—II.
Voluntary control of lid remains.
Lid reflex disappears—III (1)
Pupils constrict—III, (1)
Movement unchanged—III, (1).
Pupils in mid-constriction, movements slightly decreased—III, (
Pupils in mid-dilatation, movement abolished—III, (4).
Pupils dilated and irregular— (4) and IV
Corneal reflex disappears—III
Tear secretion depressed—III
Disappears—III, (4).

Pharynx—"Gag" reflex disappears—III, (1).
Occasionally—III, (2).

Larynx—Laryngeal reflex disappears—III, (2)

Bronchial—Cough reflex disappears III, (3) in larger bronchi and III, (4) in smaller

Heart—Rate increased (excitement)—II.
Decreases to maintenance rate—III, (1).
Rate varies.

Blood Pressure—Unchanged—I.
Increased (excitement)—II.
Return to normal—III, (1)–(2).
Fall—III, (3)–(4) and IV Due to medullary depression or effect on cardiovascular system.

Venous Pressure—No change—I.
Rises, due to increased muscle tone—II Unchanged in III. Increases in IV

Sensation—Analgesia—I (skin sensation disappears over various body areas in the following order: back, extremities, genitalia, face) Motor remains active

Deep Reflexes—Active III, (1), (2) (3)
Obtunded IV

Superficial Reflexes—Active—I Exaggerated II.
Obtunded III, (1).

EFFECTS ON RESPIRATORY SYSTEM

Cortex—Effects from psychic stimulation removed during anesthesia. Voluntary control of respiration lost. Rhythm becomes regular

Sub-cortical Centers—Effects not well-defined or studied. *May cause irregular breathing in stage II*

Medullary Centers—Respiratory center depressed in lower stage III and in IV. Respiratory center consists of formatio reticularis, group of neurons, both motor and sensory which are inter connected by fibers which control various parts of respiratory system. Cells very sensitive t CO_2 and H. Variations in sensitivity between individual neurons exist; more sensitive neurons resistant to depressant drugs. Center sends rhythmic impulses to adjacent vagal and other vital centers. Deleterious action on one center may influence other centers in medulla nd lower cord

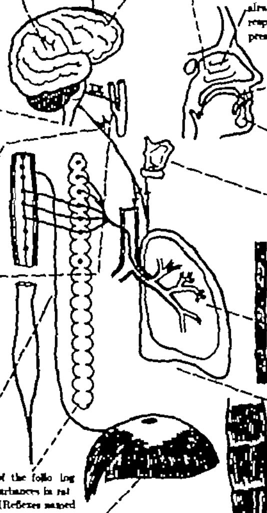
Vagus—Hering-Breuer reflex remains intact. Reflex inhibits inspiration during overdistension and inhibits expiration if negative pressure is applied to airway

Carotid-aortic Chemoreceptors—Composed of a group of cells sensitive to blood chemical changes (anoxia). Reflexly stimulates respiration when O_2 tension is lowered. Usually depressed by anesthetics. Receptor cells more resistant than cells of *respiratory center*. Apnea may result in presence of depressed medulla or acapnia when anoxic stimulus is removed with high O_2 tension.

Phrenic—Diaphragm is chief muscle of respiration. Last to be paralyzed. Controlled by sensitive neurons of center which send impulses to the phrenic nerve

Reflexes—Manipulation and stimulation of the follo ing structures during anesthesia causes disturbances in rat and rhythm of respiratory movements. (Reflexes named after structures.)

1. *Skin*—Stimulation increases rat sometimes depth.
2. *Periosteal*—Rib periosteal stimulation causes inhibition or even apnea with some gent
3. *Rectal*—Dilatation of rectal sphincter increases rate and depth, especially in light planes also stimulation of perineum and genitalia.
4. *Peritoneal*—Traction on mesentery result in spasm of larynx (Brewer-Luckhardt reflex). Frequent with traction on gallbladder stomach, spleen or kidney
5. *Perineal*—Stimulation increases rat and *depth*.
6. *Pleural*—Manipulation of pleura often inhibits respiration or causes coughing
7. *Hilar*—Stimulation of hilum or bronchi reduces coughing or *bronchial spasm*
8. *Esophageal*—Stretching or manipulation of wall causes inhibition of respiration (also arrhythmias)



Intracranial Pressure—Depressant drugs, anoxia and carbon dioxide excess increase intracranial pressure. M y indirectly affect respiration by pressure on medulla.

Mucosa—High concentrations may irritate and promote secretions. May also inhibit respiration reflexly

Muscles—Tongue and neck muscles relax and may cause airway to become obstructed. Accessory muscles of respiration connected t less sensitive neurons. Are depressed easily by most drugs.

Cilia—Ciliary activity first stimulated then halted by depressant (both volatile and non-volatile) drugs. Some drugs depress directly and cause bacteria from upper tract to pass to lower tract.

Pharynx—Stretching of muscles and pharyngeal wall by catheters and airways stimulates respiration.

Larynx—Irritating concentrations of volatile drugs, mucous, vomitus, blood and alkaline dusts produce spasm. Reflex spasms may result from stimulation of interconnecting parts of nervous system. Drugs may stimulate or depress *laryngeal nerves. Bronchial spasm may* result if stimulation is excessive.

Respiratory Exchange—Minute volume exchange decreased from decreased metabolism as well as central depression. Decreased activity decreases blood *pressure: retards venous return.*

Intercostal Muscles—Controlled by more sensitive and more resistant neurons of respiratory center. Lower intercostals paralyzed first. Reciprocal innervation exists between inspiratory and expiratory neurons so that one inhibits while the other is active

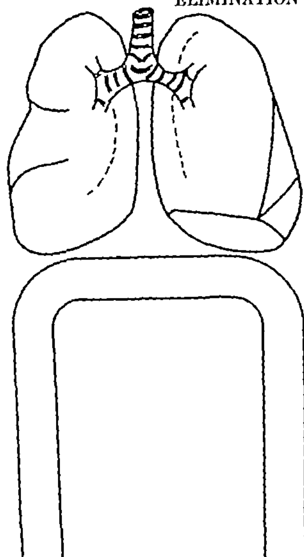
Alveolar Membrane—Not altered histologically. Local stimulation by irritating vapors and gases increases respiratory volume and rate by affecting vagal endings (ether). Volatile drugs readily pass through membrane

Abdominal Muscles—Loss of tone retards venous return t heart. Surgery of upper abdomen results in splinting of upper thorax. Decreases exchange postoperatively. May contribute to atelectasis.

Tissue Respiration—Drugs may inhibit dehydrogenases and reduce metabolic activity and oxygen consumption.

SECTION IV ADMINISTRATION OF VOLATILE DRUGS

FACTORS INFLUENCING ABSORPTION AND ELIMINATION OF VOLATILE DRUGS



Concentration of Drug in Inhaled Mixture—Usually expressed in volumes per cent or partial pressure in mm of Hg. High partial pressure establishes a steep gradient from lungs to blood and rapid saturation results. Pressure gradient reversed during recovery High concentration in blood—low in alveoli. Elimination rapid at first and gradually tapers off as pressure gradient falls.

Tidal Volume—Directly affects the amount of drug inhaled per unit time which mixes with the functional residual air Shallow breathing causes slow mixing and prolonged induction. Rapid, deep breathing hastens induction by increasing amount of drug in the alveolar air Approximately two-thirds of normal tidal volume mixed with alveolar gases.

Functional Residual Air—Represents air space in lungs in contact with alveolar surface Total volume small in children. Sudden, deep inspiration causes rapid mixing and deepening of anesthesia (or lightening if air is inhaled) Abnormally excessive in emphysema and related diseases. Mixing then occurs slowly Saturation and desaturation of blood are slowed

Solubility in Blood—Amount which dissolves in blood is in direct proportion to partial pressure Maximum amount which dissolves depends on solubility coefficient (air-blood ratio) at body temperature.

Permeability of Alveolar Membrane—Gases pass in either direction through the membrane Diffusion depends upon facility of passage of gas or vapor through a liquid. Also a selective permeability exists. Currently used drugs readily pass through and cause no histological alteration of epithelium. Secretions, fibrosis, inflammation and edema interfere with absorption of gases by reducing alveolar surface.

Blood Flow through Lung Capillaries—Not an important factor Circulation time variations are a matter of seconds and inconsequential. As maintenance proceeds an equilibrium tends to be established bet een agent dissolved in blood and that present in alveoli.

Solubility in Tissues—Adipose and other tissues of high lipoid content have greater affinity for anesthetics than other tissues.

Blood Supply to Tissues—Tissues with abundant blood supply quickly come to equilibrium with agent dissolved in blood as follows.

1. *Brain*—Contains considerable lipoid and has excellent blood supply Rapidly comes into equilibrium with blood and narcosis ensues. Patient anesthetized before other tissues are saturated. Desaturation rapid.

2. *Adipose Tissues*—Possesses poor blood supply Cells contain up to 80% lipoid material. Saturated readily Desaturated slowly causing presence of agent particularly lipophilic agent in minute amounts in blood for many hours after administration is stopped.

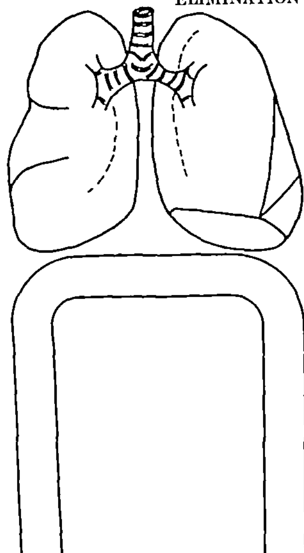
3. *Muscles and Viscera*—Possess low lipoid content but good blood supply Quickly saturated with agents of low water solubility cyclopropane. Slowly saturated by agents of higher water solubility; equilibrium with blood established slowly This type tissue acts as "buffer" and requires constant addition of agent to inhaled mixture during maintenance. Once saturation occurs desaturation is slow

4. *Bone and Connective Tissue*—Lipoid content and blood supply poor Saturation slow



SECTION IV ADMINISTRATION OF VOLATILE DRUGS

FACTORS INFLUENCING ABSORPTION AND ELIMINATION OF VOLATILE DRUGS



Concentration of Drug in Inhaled Mixture—Usually expressed in volumes per cent or partial pressure in mm of Hg. High partial pressure establishes a steep gradient from lungs to blood and rapid saturation results. Pressure gradient reversed during recovery. High concentration in blood—low in alveoli. Elimination rapid at first and gradually tapers off as pressure gradient falls.

Tidal Volume—Directly affects the amount of drug inhaled per unit time which mixes with the functional residual air. Shallow breathing causes slow mixing and prolonged induction. Rapid, deep breathing hastens induction by increasing amount of drug in the alveolar air. Approximately two-thirds of normal tidal volume mixed with alveolar gases.

Functional Residual Air—Represents air space in lungs in contact with alveolar surface. Total volume small in children. Sudden, deep inspiration causes rapid mixing and deepening of anesthesia (or lightening if air is inhaled). Abnormally excessive in emphysema and related diseases. Mixing then occurs slowly. Saturation and desaturation of blood are slowed.

Solubility in Blood—Amount which dissolves in blood is in direct proportion t partial pressure. Maximum amount which dissolves depends on solubility coefficient (air-blood ratio) at body temperature.

Permeability of Alveolar Membrane—Gases pass in either direction through the membrane. Diffusion depends upon facility of passage of gas or vapor through a liquid. Also a selective permeability exists. Currently used drugs readily pass through and cause no histological alteration of epithelium. Secretions, fibrosis, inflammation and edema interfere with absorption of gases by reducing alveolar surface.

Blood Flow through Lung Capillaries—Not an important factor. Circulation time variations are a matter of seconds and inconsequential. As maintenance proceeds an equilibrium tends to be established between agent dissolved in blood and that present in alveoli.

Solubility in Tissues—Adipose and other tissues of high lipoid content have greater affinity for anesthetics than other tissues.

Blood Supply to Tissue—Tissues with abundant blood supply quickly come to equilibrium with agent dissolved in blood as follows.

1. *Brain*—Contains considerable lipoid and has excellent blood supply. Rapidly comes into equilibrium with blood and narcosis ensues. Patient anesthetized before other tissues are saturated. Desaturation rapid.
2. *Adipose Tissue*—Possesses poor blood supply. Cells contain up to 80% lipoid material. Saturated readily. Desaturated slowly causing presence of agent particularly lipophilic agent in minute amounts in blood for many hours after administration is stopped.
3. *Muscles and Viscera*—Possesses low lipoid content but good blood supply. Quickly saturated with agents of low water solubility, cyclopropane. Slowly saturated by agents of higher water solubility; equilibrium with blood established slowly. This type tissue acts as "buffer" and requires constant addition of agent to inhaled mixture during maintenance. Once saturation occurs desaturation is slow.
4. *Bone and Connective Tissues*—Lipoid content and blood supply poor. Saturation slow.



TECHNIQUES OF ADMINISTRATION OF VOLATILE AND GASEOUS ANESTHETICS BY INHALATION

OPEN DROP TECHNIQUE

PRINCIPLE

A volatile liquid is vaporized on six to eight layers of gauze stretched over on a wire mask or similar suitable support. The vapors become mixed with air and are inhaled.

Advantages

1. Simple and uncomplicated.
2. No appreciable dead space.
3. Air is diluent and the source of oxygen.
4. No resistance to inspiration or expiration.



Disadvantages

1. O_2 tension not easily controlle[d] unless O_2 is added.
2. CO_2 tension not controllable may cause depletion (ether).
3. Variations in rate of vaporizati[on] in tension of vapor which result thesia.
4. Waste of anesthetic drug.
5. Fire hazard always present if dr[ug]
6. Irritating concentrations often stimulate flow of mucus or other
7. Attainable concentration of vap[or] event for anesthesia due to rapi[d di]lution.
8. Liquid may irritate or burn skin
9. Cold vapor reduces body temper[ature]

SEMI-OPEN TECHNIQUE

PRINCIPLE

Similar to the open mask except that mask is partly enclosed by towel or similar device to retain and increase concentrations of vapor.

Advantages

Same as open drop technique except that higher concentration of vapor more readily attained. A necessity for adults or in hot climates.



Disadvantages

Similar to open drop technique exce[pt]

1. CO_2 retained by enclosure.
2. O_2 tension may be lowered to dangerous levels.

SEMI-CLOSED TECHNIQUE

PRINCIPLE

Patient inhales through a mask attached to a reservoir (breathing bag) into which a mixture of gases and vapors of necessary composition flows steadily. Exhalations pass outward through valve attached to a mask.

Advantages

1. Oxygen enriched mixtures may be used.
2. Fixed concentration of vapor insures even plane of anesthesia.
3. Vapors and gases partly warmed.
4. Positive pressure may be used by closing valve.
5. Allows use of gaseous agents.
6. Less waste of vapors than by open method.



Disadvantages

1. Some accumulation of carbon dio[xide]
2. Some rebreathing from mask and [bag]
3. Exhaled gas wasted, may be fire [hazard]
4. Flowmeter required to measure [gases]
5. Mechanical vaporizer required [for] liquid agents.
6. Compressed gases required for mo[st]
7. Simplicity sacrificed.

CLOSED TECHNIQUE (WITH CO_2 ABSORPTION)

PRINCIPLE

Anesthetic vapors or gases are rebreathed from an entirely closed tight fitting system. CO_2 absorbed by alkali (soda lime). Constant stream of oxygen mixed with gases or vapors is supplied from flow meter.

Advantages

1. Resistance to respiration negligible.
2. Unvarying plane of anesthesia obtainable because of evenly maintained tension of drug.
3. Waste of drug is at minimum; economical.
4. Quiet and controllable respiration.
5. High humidity; decreases fire hazard.
6. Vapors and gases are warmed.
7. Positive pressure may be employed.



Disadvantages

1. Alkaline dust from absorbent may
2. Heat from reacting lime may war[m] to undesirable temperature.
3. Tight fit necessary to obtain leak[-proof] often difficult to obtain.
4. Resistance to respiration may be ex[cessive if] valves becomes defective.
5. Simplicity sacrificed for comfort.
6. "Dead space" may be excessive in baby.
7. Flowmeter and compressed gases r[equired]

INSUFFLATION

PRINCIPLE

A stream of gas or vapor combined with air or oxygen is conducted into the nasopharynx or oropharynx or



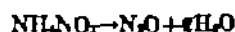
not easily controlla[ble]

SECTION V GASEOUS AGENTS

NITROUS OXIDE (NITROGEN MONOXIDE)

HISTORY—Prepared by Priestley in 1776 Anesthetic properties noted by Davy in 1799 in Chemical Journal but observation passed unnoticed Colton itinerant chemist and lecturer gave public demonstrations of it as "laughing gas in early 1840's. In 1844 Horace Wells saw demonstration and used it clinically for dental work. Gave public demonstration for dental extraction in 1845 First used clinically with oxygen by Andrews in 1868 with positive pressure by Bert in 1880 Used as preliminary to ether (gas-ether) in 1876 by Clover

PREPARATION—The commercial method employs ammonium nitrate which is heated to 240°C. The gas is collected washed and compressed to a liquid which is stored in steel cylinders. The gas must be anhydrous.



$NH_4NO_3 \rightarrow N_2O + 2H_2O$

PROPERTIES

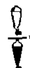
Physical—A colorless, inorganic gas possessing sweet taste and pleasant odor Non-irritating. Molecular weight 44 specific gravity 1.53 (air equals 1) Converted to colorless liquid at 0° at 1,000 pounds pressure. Boiling point—89° The gas is dispensed as a liquid under 30 atmospheres pressure Cylinders are marked blue for identification. Included in the U.S.P

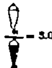
Chemical—Stable under pressure at ordinary temperatures Forms nitric oxide when heated above 450° Not inflammable but supports combustion even in absence of oxygen. Soluble in water and alcohol.

Impurities—Nitric oxide (NO) forms during manufacture: dangerous because it (1) combines with hemoglobin in same manner as carbon monoxide and causes asphyxia and (2) it combines with water to form nitric acid in the alveoli which damages alveoli and causes pulmonary edema. No impurities form at ordinary room temperature Nitrogen decreases efficiency by dilution. Oxygen or carbon dioxide may become contaminant after manufacture or opening of package.

Solubility—λ at 37°C.

Oil 1.4 Oil 1.4





= 3.2 = 3.0

H_2O .44 Blood .47

Inflammability—Not flammable when mixed with air or oxygen. Supports combustion and forms explosive mixtures when mixed with inflammable anesthetic gases and vapors even in absence of oxygen.

ADMINISTRATION

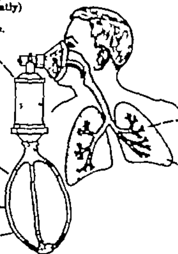
Anesthetic apparatus provided with a source of pure oxygen, flowmeters and closed or semi-closed inhalers are required. Positive pressure technique used to increase efficiency by increasing amount of drug in blood. May be given (inefficiently) by the gravity method (semi-open)

Stability in Absorber—Not altered by soda lime or baralyme.

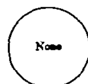
Potency—A mild anesthetic agent which rarely yields anesthesia below first plane Not efficient unless combined with narcotics or hypnotics such as morphine avertin or other depressant drugs given as preliminary medication. Difficult to obtain surgical anesthesia without premedication or sub-oxygenation. Usually fortified with ether chloroform, cyclopropane and other drugs. Anesthetic and analgesic action not due to anoxia and obtained independent of it. Effects of anoxia are additive

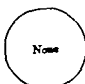
Effective Concentrations of Inhaled Mixtures—Analgesia 20 to 40% with air or oxygen; unconsciousness 35–70%, anesthesia 84–90% with oxygen Rapid acting, usually 2–3 minutes Twenty per cent yields analgesia equivalent to 10–15 mgm. morphine

Margin of Safety—Not lethal when administered with 20% or more oxygen lethal (to animals) under three atmospheres pressure even when 20% oxygen is present. Danger lies entirely in anoxia often necessary to secure surgical anesthesia.



With Air *With Oxygen*



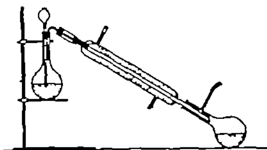


Elimination—Not altered within the body Major part eliminated through lungs unchanged within two minutes. Minute traces present in blood for several hours.

Diffusion—Passes rapidly through alveolar membranes. Collapse of isolated lung lobule with occluded bronchus and intact blood supply requires 17–65 minutes (air 18 hours) Minute amounts pass through skin during anesthesia.

SECTION V GASEOUS AGENTS

NITROUS OXIDE (NITROGEN MONOXIDE)



HISTORY—Prepared by Priestley in 1776. Anesthetic properties noted by Davy in 1799 in Chemical Journal but observation passed unnoticed. Colton, itinerant chemist and lecturer, gave public demonstrations of it as "laughing gas" in early 1840's. In 1844 Horace Wells saw demonstration and used it clinically for dental work. Gave public demonstration for dental extraction in 1845. First used clinically with oxygen by Andrews in 1868; with positive pressure by Bert in 1880. Used as preliminary to ether (gas-ether) in 1876 by Clover.

PREPARATION—The commercial method employs ammonium nitrate which is heated to 240°C. The gas is collected, washed and compressed to a liquid which is stored in steel cylinders. The gas must be anhydrous.



$$NH_4NO_3 \rightarrow N_2O + 2H_2O$$



PROPERTIES

Physical—A colorless, inorganic gas possessing sweet taste and pleasant odor. Non-irritating. Molecular weight 44; specific gravity 1.53 (air equals 1). Converted to a colorless liquid at 0° at 1,000 pounds pressure. Boiling point—89°. The gas is dispensed as a liquid under 30 atmospheres pressure. Cylinders are marked blue for identification. Included in the U.S.P.

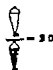
Chemical—Stable under pressure at ordinary temperatures. Forms nitric oxide when heated above 450°. Not inflammable but supports combustion even in absence of oxygen. Soluble in water and alcohol.

Impurities—Nitric oxide (NO) forms during manufacture; dangerous because it (1) combines with hemoglobin in same manner as carbon monoxide and causes asphyxia and (2) it combines with water to form nitric acid in the alveoli which damages alveoli and causes pulmonary edema. No impurities form at ordinary room temperature. Nitrogen decreases efficiency by dilution. Oxygen or carbon dioxide may become contaminant after manufacture or opening of package.

Solubility—λ at 37°C.

Oil 1.4 — Oil 1.4





H_2O .44 — Blood .47

Inflammability—Not flammable when mixed with air or oxygen. Supports combustion and forms explosive mixtures when mixed with inflammable anesthetic gases and vapors even in absence of oxygen.

ADMINISTRATION

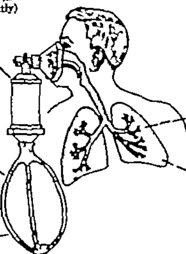
Anesthetic apparatus provided with a source of pure oxygen, flowmeters and closed or semi-closed inhalers are required. Positive pressure technique used to increase efficiency by increasing amount of drug in blood. May be given (inefficiently) by the gravity method (semi-open).

Stability in Absorber—Not altered by soda lime or baralyme.

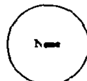
Potency—A mild anesthetic agent which rarely yields anesthesia below first plane. Not efficient unless combined with narcotics or hypnotics such as morphine, avertin or other depressant drugs given as preliminary medication. Difficult to obtain surgical anesthesia without premedication or sub-oxygenation. Usually fortified with ether, chloroform, cyclopropane and other drugs. Anesthetic and analgesic action not due to anoxia and obtained independent of it. Effects of anoxia are additive.

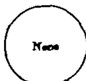
Effective Concentrations of Inhaled Mixtures—Analgesia 20 to 40% with air or oxygen; unconsciousness 35–70%; anesthesia 85–90% with oxygen. Rapid acting, usually 2–3 minutes. Twenty per cent yields analgesia equivalent to 10–14 mgm. morphine.

Margin of Safety—Not lethal when administered with 20% or more oxygen; lethal (to animals) under three atmospheres pressure even when 20% oxygen is present. Danger lies entirely in anoxia often necessary to secure surgical anesthesia.



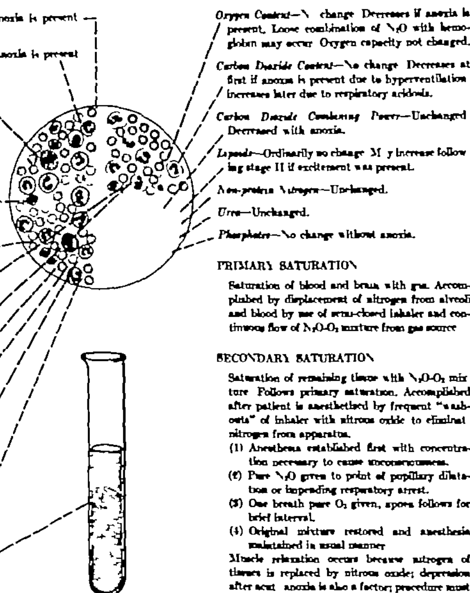
With Air — *With Oxygen*





Elimination—Not altered within the body. Major part eliminated through lungs unchanged within two minutes. Minute traces present in blood for several hours.

Diffusion—Passes rapidly through alveolar membranes. Collapse of isolated lung lobule with occluded bronchus and intact blood supply requires 17–33 minutes (air 16 hours). Minute amounts pass through skin during anesthesia.



Blood Volume—No significant change. Decreases if anoxia is present —Hemoconcentration results.

Plasma Volume—No significant change. Decreases if anoxia is present.

Red Cells—No increase in number; no increase in total hemoglobin; no change in fragility without anoxia. Drug more soluble in cells than in plasma. Number hemoglobin and cell volume percentage increases with anoxia due to constriction of spleen, decreased plasma volume and increased capillary permeability.

Leukocytes—Polymorphonuclear cells doubled in number in first 12–24 hours and return to normal after 24 hours. Relative increase in lymphocytes no change in morphology in any type cell.

Platelets—No increase in number or change in morphology or stability.

Clotting Time—No significant alteration. Prolonged clotting time may occur in the new born.

Bleeding Time—Slight insignificant prolongation. Increase due to peripheral vasodilatation.

Epinephrine—Increases with anoxia. Rapidly destroyed by enzymes of blood.

Glucose—Unchanged. Elevated with anoxia as a result of glycogenolysis.

Lactic Acid—Unchanged. Increased with anoxia from increased muscle spasm and disturbed carbohydrate metabolism.

Concentration—Solubility in plasma less than in water. Concentration varies widely but averages 65 volumes per cent. Concentration of plasma increases when administered under pressure. Most of gas disappears from blood within 3 to 6 minutes after discontinuing inhalation.

URINE

No significant changes without anoxia.

Oxygen Content—No change. Decreases if anoxia is present. Loose combination of N_2O with hemoglobin may occur. Oxygen capacity not changed.

Carbon Dioxide Content—No change. Decreases at first if anoxia is present due to hyperventilation. Increases later due to respiratory acidosis.

Carbon Dioxide Combining Power—Unchanged. Decreased with anoxia.

Lipoids—Ordinarily no change. May increase following stage II if excitement was present.

Non-protein Nitrogen—Unchanged.

Urea—Unchanged.

Phosphates—No change without anoxia.

PRIMARY SATURATION

Saturation of blood and brain with gas. Accomplished by displacement of nitrogen from alveoli and blood by use of semi-closed inhaler and continuous flow of N_2O-O_2 mixture from gas source.

SECONDARY SATURATION

Saturation of remaining tissue with N_2O-O_2 mixture. Follows primary saturation. Accomplished after patient is anesthetized by frequent "washouts" of inhaler with nitrous oxide to eliminate nitrogen from apparatus.

(1) Anesthesia established first with concentration necessary to cause unconsciousness.
(2) Pure N_2O given to point of pupillary dilatation or impending respiratory arrest.
(3) One breath pure O_2 given, apnea follows for brief interval.
(4) Original mixture restored and anesthesia maintained in usual manner.

Muscle relaxation occurs because nitrogen of tissues is replaced by nitrous oxide; depression after acute anoxia is also a factor; procedure must be repeated at varied intervals to maintain relaxation.

PATHOLOGY

No specific gross or histo-pathological changes due to nitrous oxide itself occur. Changes due to anoxia are found in nervous and other tissues.

USES

(1) For major surgery in combination with basal narcotic drugs such as avertin, pentothal, morphine-scopolamine, etc.
(2) As preliminary or induction agent for ethyl ether or trichlorethylene.
(3) For minor surgery which does not necessitate profound anesthesia.
(4) For analgesia in dentistry and obstetrics.
(5) When non-inflammable agents are required.

CONTRAINDICATIONS

None provided no muscle relaxation is required and stage III is secured with no anoxia.

ADVANTAGES

(1) It is non-inflammable.
(2) Non-irritating and pleasant to the patient.
(3) Induction and recovery are rapid.
(4) Has no deleterious action on circulatory, respiratory or other systems and organs.
(5) Is an excellent general analgesic.
(6) Inexpensive compared to many other drugs.
(7) Post-anesthetic nausea and vomiting unusual.

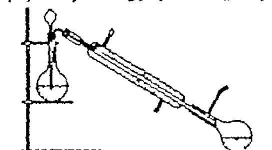
DISADVANTAGES

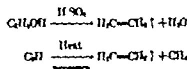
(1) Concentration necessary to produce stage III causes suboxygenation unless combined with a basal or some more potent agent.
(2) Relaxation of muscles inadequate for general surgery.
(3) Asphyxia is always a hazard.
(4) Some form of apparatus necessary for metering gases.

ETHYLENE

HISTORY—Prepared by Becher in 1669(?) Anesthetic properties first noted by Hermann in 1865 Crocker and Knight in 1908 noted toxicity to plants Luckhardt and Carter of Chicago introduced it in 1923 as an anesthetic for animals and man First clinical study by Isabella Herb 1924 in Chicago. Cotton in 1917 used ethylenated ether also investigated by W E. Brown in 1924

PREPARATION—(1) The usual method of preparation is to dehydrate ethyl alcohol with sulphuric or phosphoric acid. (2) Also prepared by cracking propane The gas is purified liquefied and stored in steel cylinders.





PROPERTIES

Ethylene is an unsaturated gaseous hydrocarbon. It is the simplest member of the olefine series.

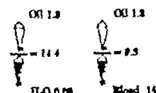
Physical—A colorless non-irritating gas, possessing an ethereal odor and taste Molecular weight 28 specific gravity 0.97 (air equals 1) Liquefies at 10°C at 60 atmospheres pressure; boiling point −103°C Highly inflammable

Chemical—Stable under ordinary circumstances does not polymerize when stored under pressure in metal cylinders. Adds halogens to form organic halides and acids to form salts. Decolorizes solutions of permanganates.

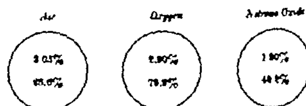
Impurities—Other hydrocarbons, such as methane propane acetylene carbon monoxide phosphene hydrogen sulphide sulphur dioxide May be contaminated with carbon dioxide nitrogen or oxygen after manufacture Most dangerous impurity is carbon monoxide The minutest traces inhaled over a prolonged period during anesthesia causes asphyxia by combining with hemoglobin.

Potency—Somewhat more potent than nitrous oxide Rarely yields anesthesia below first plane Muscle relaxation poor Requires basal of morphine avertin, pentothal or other depressant drugs to produce non-asphyxial surgical anesthesia. Effect of anoxia are additive Ether cyclopropane and other inhalation agents produce additive effects. May be used with curare to obtain muscle relaxation.

Solubility λ at 37°C.



Inflammability—Flash point below 32°F; 1 pound yields 292 cubic feet of inflammable mixture with air at 68°F at standard pressure Minimum ignition temperature in air 914°F In oxygen 905°F Combustion supported by nitrous oxide Anesthetic and analgesic concentrations are inflammable Helium nitrogen and carbon dioxide act as quenching agents but are unsuitable because of anoxia or carbon dioxide excess.



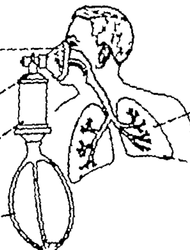
ADMINISTRATION

Apparatus equipped with flowmeter either semi-closed or closed inhalers are necessary Closed methods safest because of fire hazard. A source of pure oxygen is necessary Semi-closed method mandatory for induction to eliminate nitrogen.

Effective Concentrations—Analgesia, 20-40%; unconsciousness 60% anesthesia 75-80% Induction rapid, requiring 2 to 3 minutes

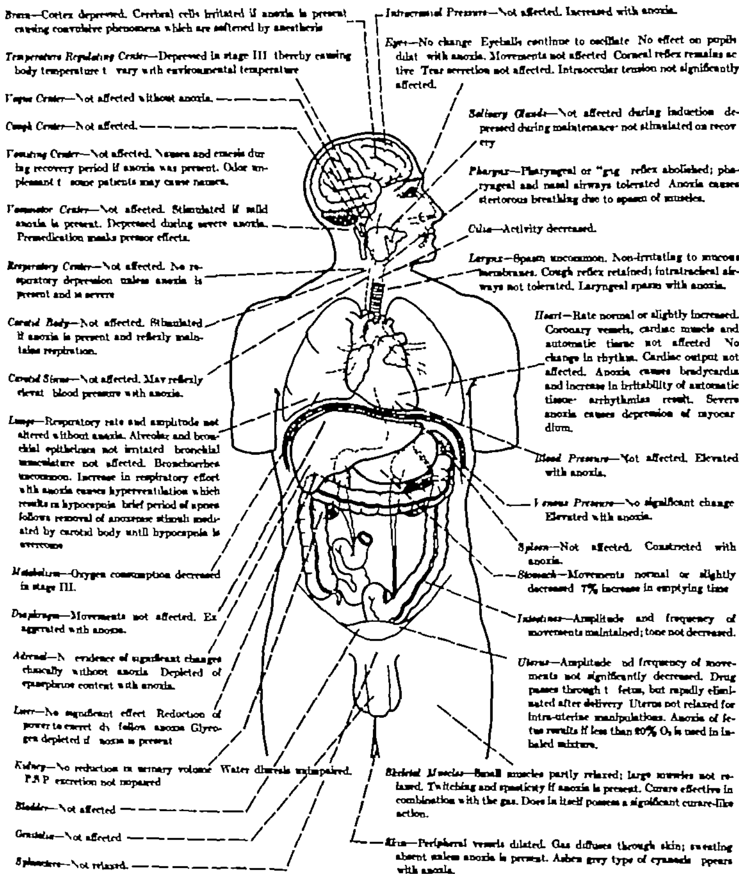
Stability in Absorber—Not altered by soda lime or baralyme or heat generated in canister

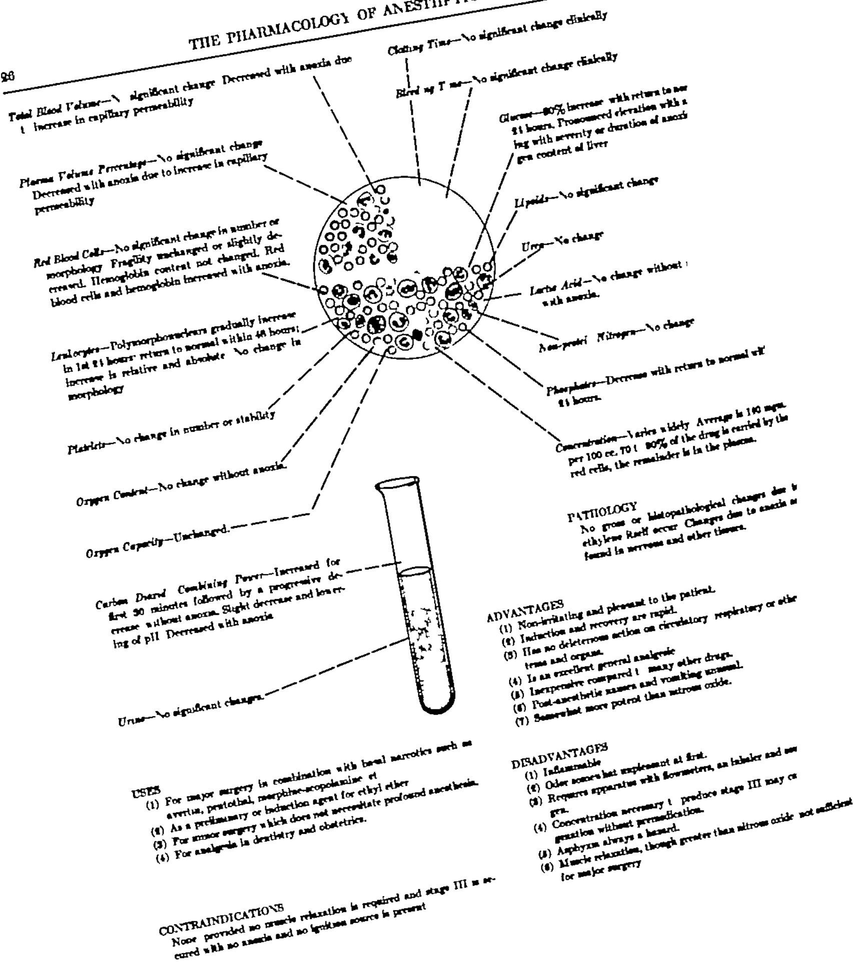
Margin of Safety—Not lethal unless anoxygenation is present. Lethal in 70-80% O_2 mixture to mice at 2 atmospheres pressure Greatest hazards in clinical use are anoxia and inflammability



Elimination—Not altered or combined in body with any tissue Major portion eliminated in exhalations within two minutes. A lipophilic anesthetic which has great affinity for lipoid tissues. Complete desaturation from fat deposits requires several hours Minute traces detectable in blood for hours after conclusion of anesthesia.

Diffusion—Disappears from isolated lung lobule with blood supply intact and bronchus occluded in 15-60 minutes (air=18 hours). Passes through skin .0018 mgm. per square cm. per hour


Brain—Cortex depressed. Cerebral cells irritated if anoxia is present causing convulsive phenomena which are softened by anesthesia
Temperature Regulating Center—Depressed in stage III thereby causing body temperature to vary with environmental temperature
Vagus Center—Not affected without anoxia.
Cough Center—Not affected.
Vomiting Center—Not affected. Nausea and emesis during recovery period if anoxia was present. Odor unpleasant to some patients may cause nausea.
Vasomotor Center—Not affected. Stimulated if mild anoxia is present. Depressed during severe anoxia. Premedication masks pressor effects.
Respiratory Center—Not affected. No respiratory depression unless anoxia is present and is severe
Carotid Body—Not affected. Stimulated if anoxia is present and reflexly maintains respiration.
Carotid Sinus—Not affected. May reflexly elevate blood pressure with anoxia.
Lungs—Respiratory rate and amplitude not altered without anoxia. Alveolar and bronchial epithelium not irritated bronchial musculature not affected. Bronchorrhea uncommon. Increase in respiratory effort with anoxia causes hyperventilation which results in hypocapnia brief period of apnea follows removal of anoxemic stimuli mediated by carotid body until hypocapnia is overcome
Metabolism—Oxygen consumption decreased in stage III.
Diaphragm—Movements not affected. Exaggerated with anoxia.
Adrenal—No evidence of significant changes clinically without anoxia Depleted of epinephrine content with anoxia.
Liver—No significant effect Reduction of power to excrete dye follow anoxia Glycogen depleted if anoxia is present
Kidney—No reduction in urinary volume Water diuresis unimpaired. P.S.P. excretion not impaired
Bladder—Not affected
Genitalia—Not affected
Sphincters—Not relaxed.
Intracranial Pressure—Not affected. Increased with anoxia.
Eyes—No change Eyeballs continue to oscillate No effect on pupils dilate with anoxia. Movements not affected Corneal reflex remains active Tear secretion not affected. Intraoccular tension not significantly affected.
Salivary Glands—Not affected during induction depressed during maintenance not stimulated on recovery
Pharynx—Pharyngeal or "gag" reflex abolished; pharyngeal and nasal airways tolerated Anoxia causes stertorous breathing due to spasm of muscles.
Cilia—Activity decreased.
Larynx—Spasm uncommon. Non-irritating to mucous membranes. Cough reflex retained; intratracheal airways not tolerated. Laryngeal spasm with anoxia.
Heart—Rate normal or slightly increased. Coronary vessels, cardiac muscle and automatic tissue not affected No change in rhythm. Cardiac output not affected. Anoxia causes bradycardia and increase in irritability of automatic tissue arrhythmias result. Severe anoxia causes depression of myocardium.
Blood Pressure—Not affected. Elevated with anoxia.
Venous Pressure—No significant change Elevated with anoxia.
Spleen—Not affected. Constricted with anoxia.
Stomach—Movements normal or slightly decreased 7% increase in emptying time
Intestines—Amplitude and frequency of movements maintained; tone not decreased.
Uterus—Amplitude and frequency of movements not significantly decreased. Drug passes through to fetus, but rapidly eliminated after delivery Uterus not relaxed for intra-uterine manipulations. Anoxia of fetus results if less than 20% O_2 is used in inhaled mixture.
Skeletal Muscles—Small muscles partly relaxed; large muscles not relaxed. Twitching and spasticity if anoxia is present. Curare effective in combination with the gas. Does in itself possess a significant curare-like action.
Skin—Peripheral vessels dilated. Gas diffuses through skin; sweating absent unless anoxia is present. Ashen grey type of cyanosis appears with anoxia.



PATHOLOGY

No gross or histopathological changes due t ethylene itself occur. Changes due to anoxia a found in nervous and other tissues.

ADVANTAGES

(1) Non-irritating and pleasant to the patient.
(2) Induction and recovery are rapid.
(3) Has no deleterious action on circulatory, respiratory or othe tems and organs.
(4) Is an excellent general analgesic.
(5) Inexpensive compared to many other drugs.
(6) Post-anesthetic nausea and vomiting unusual.
(7) Somewhat more potent than nitrous oxide.

DISADVANTAGES

(1) Inflammable
(2) Odor somewhat unpleasant at first.
(3) Requires apparatus with flowmeters, an inhaler and sou gen.
(4) Concentration necessary to produce stage III may ca genation without premedication.
(5) Asphyxia always a hazard.
(6) Muscle relaxation, though greater than nitrous oxide, not sufficient for major surgery.

USES

(1) For major surgery in combination with basal narcotics such as avertin, pentothal, morphine-scopolamine, etc.
(2) As a preliminary or induction agent for ethyl ether.
(3) For minor surgery which does not necessitate profound anesthesia.
(4) For analgesia in dentistry and obstetrics.

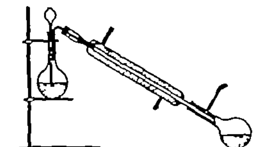
CONTRAINDICATIONS

None provided no muscle relaxation is required and stage III is secured with no anoxia and no ignition source is present.

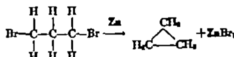
CYCLOPROPANE

HISTORY—First prepared by the German chemist August von Freund in 1882. Anesthetic properties discovered on animals by V. E. Henderson and G. H. W. Lucas of Toronto in 1920. First clinical report by Ralph Waters in 1933 at the University of Wisconsin.

PREPARATION—(1) By treating 1,3-di-brom propane (Freund's method) with zinc (2) from 1,3-di-chlor propane (Haas). The ring is thereby completed.

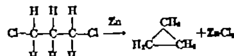


(1)



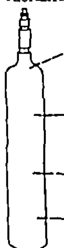
$$Br-CH_2-CH_2-CH_2-Br \xrightarrow{Zn} (CH_2)_3 + ZnBr_2$$

(2)



$$Cl-CH_2-CH_2-CH_2-Cl \xrightarrow{Zn} (CH_2)_3 + ZnCl_2$$

PROPERTIES



Physical—A colorless gas possessing a sweet odor and taste. Non-irritating. Molecular weight 42.08, specific gravity 1.46 (air equals 1). *Liquefies* at approximately 5 atmospheres pressure at room temperature; boiling point −34°C. Included in the U.S.P. XIII. 1 oz. vap. equals 4.20 gals. Also known as trimethylene.

Chemical—A saturated cyclic hydrocarbon isomeric with propylene. Does not polymerize as stored under ordinary circumstances. Forms propylene at 100°C. with iron catalyst. Absorbed by sulphuric acid. Does not decolorize permanganate solutions.

Storage—In steel alloy cylinders. Stable under ordinary conditions of storage.

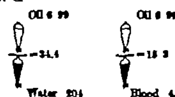
Impurities—Propylene, propane, allene, organic halides, cyclohexane may be present from manufacture. Inorganic gases such as nitrogen, carbon dioxide, and oxygen may contaminate after manufacture.

Solubility λ at 37°C.

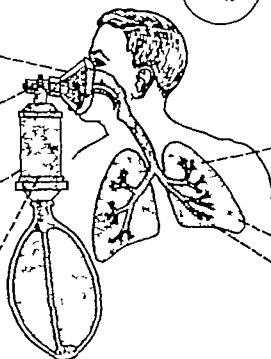
Oil 6 99 — −34.4 — Water 204

Oil 6 99 — −18 3 — Blood 457

Inflammability—Highly flammable. Flash point below 0°C., 1 pound mixed with air yields 376 cubic feet of explosive mixture at 60°F and atmospheric pressure. Ignition temperature (minimum) 905°F in air—849°F in oxygen.



With Air	*With Oxygen*	*With Nitrous Oxide*
2.4%	2.48%	1.6%
10.3%	60.0%	30.3%



Average Concentrations of Inhaled Mixtures—Analgesia 3 to 5%. Unconsciousness 6 to 8%. Plane 1, 1 to 7%. Plane 2, 7 to 14%. Plane 3, 14 to 25%. Plane 4, 25 to 40% (respiratory failure).

Induction Time—Rapid, 2 to 3 minutes. Possesses low solubility coefficient (air/blood ratio).

ADMINISTRATION

By closed system only. Open or semi-semi-closed too costly and hazardous. May be given by insufflation to infants—costly and hazardous.

Stability in Absorber—Not altered by alkaline carbon dioxide absorbents.

Elimination—Recovery with return of reflexes occurs within 3 to 10 min. Not altered or combined in body. *Major part* eliminated in exhalations within 10 min. Complete desaturation requires several hours. Minute amounts detectable in blood for several hours after recovery. Minute amounts diffuse through the skin. Gas passes into gastrointestinal tract, air collections in pleura and other hollow viscera.

Diffusion—Rapid from isolated lung lobule. Passes through rubber.

Effect on Tissues—No histological changes characteristic of drug occurs in any organ, including heart.

Cortex—Depressed. Yields all planes of anesthesia. Cortical potentials depressed (see electroencephalogram) Six levels.

Hypothalamus—Reflexly stimulated by afferent impulses from mesentery efferent impulses via cervical sympathetics reflexly sensitize heart.

Heat regulating center—Depressed. Body temperature may fall in cool environment.

Vasomotor Center—Not significantly affected. Increased carbon dioxide tension may stimulate and cause hypertension during anesthesia. Peripheral resistance increased.

Respiratory Center—Depressed in plane 3 & 4. Respiration ceases before circulation in overdosage

Vomiting Center—Depressed in third stage. Nausea common during recovery or during analgesia (stage I)

Cough Center—Depressed in third stage

Carotid Body—Not affected. Possible stimulation

Carotid Sinus—Remains active

Lungs—Minute volume exchange decreases particularly in planes 3 & 4. Non-irritating to the respiratory tract. Apnoea easily induced by hyperventilation particularly with morphine premedication. Hering-Breuer reflex remains active. Carbon dioxide tension increased. Stretch and deflation receptors sensitized but not enough to increase ventilation.

Bronchi—Bronchial tone increased. Bronchial spasm easily induced. Hilar stimulation causes coughing. Atropine minimizes intensity of spasm.

Metabolism—Oxygen consumption decreased in stage III. Respiratory acidosis common.

Diaphragm—Excursions reduced during deep anesthesia.

Adrenal—Probably not affected. Endogenous epinephrine released from gland. Bilateral extirpation causes abolition of arrythmias. Blood norepinephrine increased

Liver—No evidence of dysfunction demonstrated by dye tests. Bile flow increased. No histological changes following prolonged or repeated use.

Kidney—Urine formation suppressed during anesthesia. Renal vasoconstriction causes decreased blood flow and filtration. Oliguria results. Volume increased in recovery period due to compensatory polyuria. No effect on renal parenchyma.

Ureters—Decreased tone.

Bladder—Decreased tone. Incidence of post operative urinary retention differs little from other gases.

Genitalia—No significant effect. Priapism noted occasionally

Autonomic Nervous System—Effects suggestive of parasympathetic stimulation appear in respiratory system, circulatory system, eye, and gastrointestinal tract. Impulses sensitizing heart believed to pass from hypothalamus via cervical sympathetics.

Intracranial Pressure—Changed little clinically. May increase if respiratory depression is present.

Eyes—Pupils constricted and remain so through deeper planes. Dilate i stage IV, or if anoxia is present. Lacrimation common during seco and third plane. Fixation of eyeballs in second to third plane. Musc paralyzed in third plane. Corneal reflex disappears in third plane.

Mucous Membranes—No irritation ordinarily. Irrita with more than 80% concentration. Secretions common. Activity of cilia decreased or inhibited com pletely

Salivary Glands—Stimulated during induction and in recovery period. Depressed during surgical anesthesia. Excessive secretions not common.

Larynx—Laryngeal spasm common, particularly when concentration exceeds 80%. Laryngeal reflex abolished in second plane.

Heart—No significant effect on myocardium during surgical anesthesia in stages I, II and III. Depressed in stage IV. Cardiac output unchanged or increased. Decreased in stage IV. Decreased with narcotic premedication. Rate decreased. Bradycardia common. Increases irritability of automatic tissue causing arrythmias from displaced pacemaker. Vagus escape, a-v block, ventricular tachycardia, or other arrythmias occur spontaneously. May occur at any time but more often with deep anesthesia. Irritability of automatic tissue enhanced further by epinephrine and related amines. Ventricular fibrillation may be induced in irrita ble hearts. Ether (4%) prevents as well as procaine intravenously. Irregularities increase as CO_2 is retained.

Blood Pressure—Little changed without respiratory depression. Usually elevated, particularly systolic phase in deeper planes. May fall to shocklike levels at conclusion of anesthesia due to sudden release of CO_2

Venous Pressure—Central venous pressure elevated in deep anesthesia.

Spleen—Variable in size; may increase two three times.

Stomach—Hunger contractions lessen. Emptying time decreased 75%. Gastric tone normal. Gastric secretion increased during light and decreased during deep anesthesia.

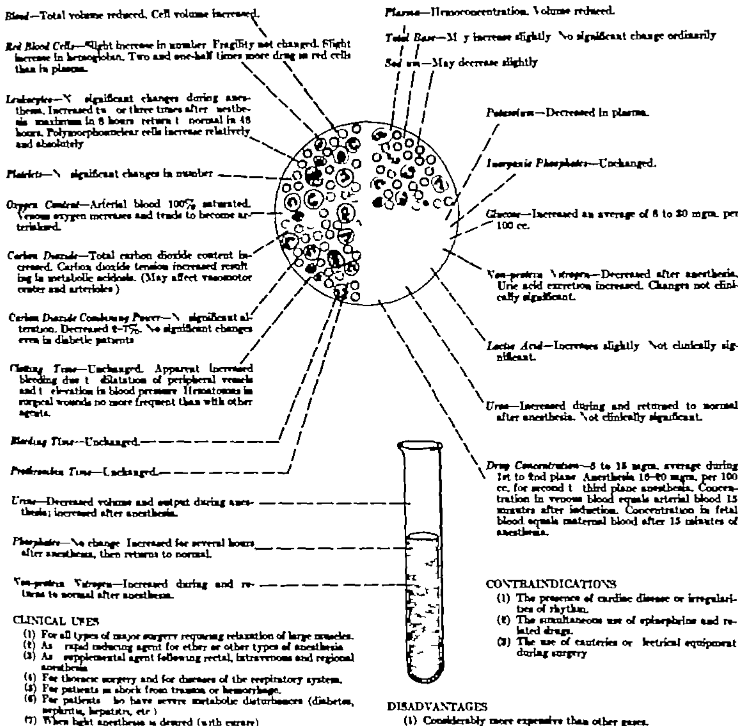
Intestines—Activity decreased in deep anesthesia. Peristalsis decreased but present in light anesthesia, circular and propulsive movements both decrease in third plane. Rapid recovery of tone and movements when agent is withdrawn. Areas from which afferent impulses arise probably located in mesentery and transmitted to hypothalamus via sympathetics.

Uterus—Contractions mildly depressed in light anesthesia. Abolished in 3rd plane. Intra-uterine pressure decreased. Drug passes through placenta to fetus. Oxygen content decreased in fetal arterial blood approximately 80%. Depression of respiration of newborn frequent. Pitocin and vasopressin can be used.

Skeletal Muscles—Adequate muscle relaxation obtainable. Large muscles relaxed in third plane. Small muscles in second plane. Little loss of muscle tone in first plane. Effective with curare. Does not possess marked curare-like action.

Skin—Temperature increased. Gas diffuses through skin. Peripheral ar terioles dilate. Venous blood becomes arterialized, giving rise to redd color

Tissues—No definite pathological changes ascribable to drug in any tiss including brain and heart.



CLINICAL USES

(1) For all types of major surgery requiring relaxation of large muscles.
(2) As rapid inducing agent for ether or other types of anesthesia.
(3) As supplemental agent following rectal, intravenous and regional anesthesia.
(4) For thoracic surgery and for diseases of the respiratory system.
(5) For patients in shock from trauma or hemorrhage.
(6) For patients who have severe metabolic disturbances (diabetes, nephritis, hepatitis, etc.)
(7) When light anesthesia is desired (with curare).

ADVANTAGES

(1) Possesses wide margin of safety.
(2) Yields anesthesia in all planes.
(3) Induction is pleasant and rapid.
(4) Salivation or bothersome secretions are absent.
(5) Respiration is quiet, diaphragmatic movements not exaggerated.
(6) Labile—allows immediate lightening and deepening of anesthesia.
(7) Apnea is easily induced, facilitating controlled respiration when indicated.
(8) Does not disturb metabolic processes and blood chemical patterns significantly.
(9) Recovery is rapid.

CONTRAINDICATIONS

(1) The presence of cardiac disease or irregularities of rhythm.
(2) The simultaneous use of epinephrine and related drugs.
(3) The use of cauteries or electrical equipment during surgery.

DISADVANTAGES

(1) Considerably more expensive than other gases.
(2) Forms highly explosive mixtures with air or oxygen in anesthetic concentrations.
(3) Increases irritability of cardiac automatic tissue predisposing to arrythmias.
(4) Adequate muscle relaxation not obtained consistently.
(5) Oozing and capillary bleeding frequently encountered.
(6) Hypertension often encountered.
(7) Laryngeal spasm during induction and recovery common.
(8) Emergence delirium frequent during recovery.
(9) Post anesthetic nausea occurs frequently.
(10) Respiratory depression and troublesome apnea common.
(11) Post anesthetic hypotension (cyclopropane shock) often observed in long operations.
(12) Carbon dioxide tension increased, causing metabolic acidosis.

LESSER KNOWN HYDROCARBONS

	Methane	Ethane	Propane	Butane	Isobutane	Propylene	Alpha Butylene
History	Richardson in 1867 studied its action.	Studied by Richardson.	Studied by Brown and Henderson.	Studied by Stoughton and Lamson.	Studied by Stoughton and Lamson.	Investigated by Davidson, Halsey, Reynolds & Cohen.	Brown and Henderson used it in small amounts.
Chemical structure	Saturated hydrocarbon.	Saturated hydrocarbon.	Saturated hydrocarbon	Saturated hydrocarbon.	Branched chain saturated hydrocarbon.	Unsaturated hydrocarbon.	Unsaturated hydrocarbon. Also known as ethyl ethylene.
Chemical formula	CH_4 (H–C–H with H above and below)	H₃C–CH₃ structural formula	H₃C–CH₂–CH₃ structural formula	H₃C–CH₂–CH₂–CH₃ structural formula	$(CH_3)_2CH–CH_3$ structural formula	$CH_3C(H)=CH_2$	H–C–C–C–C– structural formula
Properties	Colorless, somewhat odorless gas. M.W 16. B.P −160°C.	Colorless, tasteless gas. M.W 30. B.P −88°C.	Colorless gas. M.W 44. B.P −37°C.	Colorless gas. M.W 58. B.P −5°C.	Colorless gas. M.W 58. B.P −10°C.	Colorless gas. Odor similar to ethylene. M.W 42. Isomer of cyclopropane. Stable but difficult to purify. Oil water ratio [illegible].	More potent than propylene. Potency of hydrocarbons increases ... as M.W increases
Potency	Feebly narcotic. 80–90% required for effect. Anoxia is chief hazard.	Not much greater than that of methane.	Not much more potent than methane.	Feebly narcotic. Greater than propane.	Less potent than butane.	More potent than ethylene. Not as potent as cyclopropane.	More potent than propylene.
Inflammability	Highly inflammable.	Highly inflammable.	Highly inflammable.	Highly inflammable.	Highly inflammable.	2–[illegible]% in air 2–[illegible]% in oxygen is explosive.	[illegible]% in air, [illegible]% in oxygen is explosive.
Concentration for anesthesia	Over 80% needed for unconsciousness.	Not studied.	90% inhaled mixtures required for narcosis.	20–25% Possesses narrow margin of safety.	45% necessary for anesthesia, 55% lethal.	Anesthesia 50–80%. 70–90% respiratory failure.	[illegible]% for anesthesia and [illegible]% respiratory arrest.
Absorption and elimination	Eliminated unchanged through lungs.	Eliminated unchanged through lungs.	Eliminated unchanged through lungs.	Eliminated unchanged through lungs.	Eliminated unchanged through lungs.	Induction rapid, 3 min. Eliminated unchanged through lungs.	Eliminated unchanged through lungs.
Circulatory effects	Not known. Mostly effects of anoxia are noted.	Not studied.	Not studied.	Not studied.	Not studied.	Arrythmias and fall in blood pressure follow use of high concentrations.	Causes fall in blood pressure in surgical a[nesthesia].
Respiratory effects	Mostly result of anoxia.	Results of anoxia.	Concentrations as low as 30% cause respiratory failure.	Not reported.	Not reported.	Respiratory failure occurs before circulatory. Exaggerated respiratory activity common.	
Metabolic and other effects	Not reported.	Not studied.	None reported.	Not reported.	Not reported.	Vomiting common. Little effect on blood sugar. Lowered pH of blood.	Causes muscle rig[idity]
Method of administration	Inhalation by semi-closed technique.	Inhalation by semi-closed technique.	Inhalation by semi-closed technique.	Inhalation by semi-closed technique	Inhalation by semi-closed system.	Closed system with oxygen.	Closed system with oxygen.
Usefulness	Not clinically useful.	Not clinically useful.	Not clinically useful.	Not clinically useful	Not clinically useful.	Not useful. Pure specimens may offer promise of use.	Not clinically u[seful]

	Beta Butylene	Gamma Butylene	Amylene	Allene	Butadiene	Acetylene	Methyl Cyclopropane	Cyclobutane
History	Schmidt and Schoeman studied it in 1929.	Killian studied it on rabbits.	Investigated by Snow 1857	Schmidt and Schoeman studied its effects.		Studied by Wieland. Known as Narcylene. Lighter than air S.G. 91. Oil water ratio 1.1 at 37°C.	Henderson studied their effects in animals in 1937	Synthesized and studied by Krantz in 1948.
Chemical structure	Olefine.	Olefine.	Olefine.	Olefine.	Olefine.	Acetylene.	Cyclic hydrocarbons.	
Chemical formula	$H_3C-CH=CH-CH_3$	$CH_2=C(CH_3)_2$	$CH_2=C(C_2H_5)(CH_3)$	$H_2C=C=CH_2$	$H_2C=CH-CH=CH_2$	$HC\equiv CH$	H CH₃ / C / H₂C—CH₂ ; H—CH₃ / C / H₃C C—CH₃ / H ; H CH₃ / C / C—C / H CH₃ H CH₃	H_2C-CH_2 H_2C-CH_2
Properties	Unpleasant smelling gas. B.P. 1.0°C. M.W. 56. Oil water ratio 100.0. Also known as [illegible]-butylene.	B.P. −6°C. M.W. 56.	Colorless liquid. Boils at [illegible]°C. Unstable. Polymerizes to higher molecular weight hydrocarbons.	A diolefine. Colorless gas with sour taste. M.W. 40. B.P. −[illegible]° Oil water ratio 17 at 37°C. Polymerizes in storage.	Colorless gas with disagreeable odor. Unstable. Oil water ratio 107.0.	Colorless gas with pungent unpleasant odor and bitter after taste. Explodes spontaneously at two atmospheres pressure. Stored in cylinders containing asbestos soaked with acetone.	Colorless gases. mono- / di- / tri- } methyl cyclopropane	Colorless gas possessing odor like cyclopropane. Insoluble in water, soluble in oils.
Potency	More potent than propylene. Potency increases almost in geometric ratio as M.W. increases.	More potent than propylene.	More potent than propylene or butylene	More potent than acetylene.	More potent than allene.	Slightly more potent than ethylene.	More potent than cyclopropane (all three). Potency increases with M.W. of each agent.	More potent than cyclopropane.
Inflammability	[illegible]% in air.	[illegible]% in air [illegible]% in oxygen.	Inflammable.	Inflammable.	Inflammable.	2.5–80% in air 2.8–93% in oxygen.	Inflammable.	Inflammable.
Concentration for anesthesia	[illegible]% yields anesthesia. [illegible]% lethal.	[illegible]% yields anesthesia.	6% yields anesthesia.	[illegible]% gives incomplete narcosis [illegible]% lethal.	10–15% for narcosis. Narrow margin of safety	Anesthesia [illegible]%. First plane [illegible]%. Second plane [illegible]%.	15% mono-methyl, 10% di-methyl, 7% tri-methyl. [illegible]% required for induction. Induction and recovery rapid.	
Absorption and elimination	Eliminated unchanged through lungs.	Eliminated unchanged through lungs.	Eliminated unchanged through lungs.	Eliminated unchanged through lungs.	Through the lungs unchanged.	Rapidly absorbed. Induction requires 2–3 min. Not changed in body. Eliminated unchanged—[illegible]% in [illegible].	Presumably eliminated unchanged through lungs.	Through lungs probably unchanged.
Circulatory effects	Arrhythmias and depression of cardiac automaticity occurs.	Arrhythmias, tachycardia and fall in blood pressure common.	Arrhythmias frequent.	Pulse rate increased. Blood pressure elevated.	Tachycardia, arrhythmias and increase in blood pressure.	Causes rise in blood pressure. Vasomotor center stimulated. Pulse slowed reflexly. [illegible] volume increases.	Increased muscle tone and fibrillation. Severe cardiac disturbances.	Somewhat like cyclopropane. Sensitizes heart to epinephrine causing arrhythmias.
Respiratory effects	Causes hyperventilation and pulmonary irritation.	Causes hyperventilation and pulmonary irritation.		Rate and depth increased.	Causes marked hyperventilation.	Respiration does not fail unless anoxia is present. Does not yield anesthesia deeper than third plane. Non-irritating.		Similar to cyclopropane.
Metabolic and other effects			Not studied.			Does not damage tissues. Decreases CO_2 combining power. Some elevation in blood sugar. No effect on blood cells.		Similar to cyclopropane.
Method of administration	Closed system with oxygen.	Closed system with oxygen.	Inhalation or intravenously	By inhalation.	By inhalation.	Closed or semi-closed system. Acetone must be removed by washing or adsorption with charcoal.	Administered by inhalation.	By inhalation in closed system.
Conclusions	Not clinically useful.	Not clinically useful.	Not clinically useful.	Not clinically useful.	Not clinically useful.	Does not yield satisfactory muscle relaxation. Anoxia may occur. Does not cause respiratory failure without anoxia. Used to determine cardiac output.	Not useful clinically	Has been used in man. Behaves like cyclopropane.

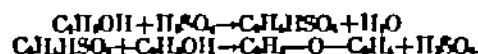
Name	Cyclopentane	Cyclohexane	Spiropentane	Kerosene	Sulphur hexafluoride
History	Studied by Virtue 1940	Studied by Virtue 1940	Studied by Summers 1950		Studied by Virtue an[d] Weaver 1948.
Chemical structure	Saturated cyclic hydrocarbon. CH_2—CH CH_4 CH_2—CH	Hexa-hydrobenzene from petroleum. CH_2 CH_2 CH_2 CH CH_2 CH	A hexane cyclic hydrocarbon 2 cyclopropanes. CH_2—CH C CH_2—CH_4	Mixture of hydrocarbons from petroleum 175°–275°C fraction. —	Sulphur with six f[luo]rine atoms. Very sta[ble] SF
Properties	Mobile, clear liquid, B.P 49.2°C. S.G. 0.7460 at 20° Refract. 1.4068 at 20°	Mobile clear liquid. B P 80.8°C. S G 0.7781 at 20°C.	Mobile liquid B P 39.03 Refract. 1.4122 at 20°	Olefines and aromatics removed	Gaseous agent. Inert, stable. Highly insoluble in water 0.1%—He 0.87
Potency	Seven times more than cyclopropane (.07 versus .005 mole)	Cyclopropane (.07 versus .018 moles)	More potent than cyclopropane	Varies with source	Less potent than nitrous oxide. Probably due to low water solubility
Inflammability	Flammable	1.3%–8.4% by vol in air Flash Point 26°	Flammable	Flammable	Not flammable.
Concentration	8% anesthetic index 1.56.	3-6% anesthetic index 1.82.	3-8% anes 7% resp failure.		79%–21% O_2 Very i… ert.
Absorption and elimination	By inhalation. Presumably unchanged in body	By inhalation.	Induction 3-5 mins. Recovery 5-10 minutes.	Absorbed slowly from bowel. Eliminated slowly. Requires days.	By inhalation with o… gen.
Circulatory effect	Arrhythmias. Sensitizes heart to epinephrine	Similar to cyclopentane, but more toxic	B P falls. Tachycardia, myocardial depression	Depresses heart. Pulmonary edema results.	No remarkable eff…
Metabolic effects	Not studied. Causes twitching and convulsive movements.			Toxic to liver kidney	
Method of administration	Volatilizes. Vapor inhaled.	By inhalation.	By inhalation with oxygen.	Not used. Accidental poisoning	By inhalation
Usefulness	Toxic manifestations limit clinical usefulness.	Not clinically useful. Produces neuromuscular manifestations.	Not clinically useful. Produces convulsive manifestations.	Depression of C.N.S. occurs, also pulmonary edema.	Not potent used alone. Not clinically useful. Not effective in animals.

SECTION VI. VOLATILE AGENTS

ETHYL ETHER

HISTORY—Synthesis described by Valerius Cordus (Germany) in 1540 who called it "sweet vitriol." Paracelsus (Switzerland) in 1540 mentioned pain relieving qualities. Named "ether" by Frobenius (Germany) in 1730. Richard Pearson (England) in 1794 used inhalations for treatment of phthisis. Report of deep sleep induced by ether reported by Beddoes in 1794. Michael Faraday in 1818 recorded stupifying effects of the compound. W. E. Clark (U. S.) in 1842 administered it in extraction of a tooth. Used clinically several months later by Crawford W. Long in 1842 after having experience with "ether frolics" in Athens, Georgia. In 1805 John C. Warren (U. S.) used ether to relieve last stages of pulmonary inflammation. Charles T. Jackson (U. S.) in 1846 suggested its use to Morton who removed a tooth successfully with it. First public demonstration by William T. G. Morton in 1846 in Boston. Used as a surgical anesthetic by Morton for removal of tumor of jaw by Dr. J. C. Warren in 1846. John Snow in 1847 was first physician anesthetist to use ether at St. George's hospital, London. Originally called "letheon" by Morton.

PREPARATION—Most common method is to dehydrate ethyl alcohol with sulphuric acid below 140°C.



$$C_2H_5OH + H_2SO_4 \rightarrow C_2H_5HSO_4 + H_2O$$
$$C_2H_5HSO_4 + C_2H_5OH \rightarrow C_2H_5\text{—}O\text{—}C_2H_5 + H_2SO_4$$

PROPERTIES

Physical—A colorless, highly volatile liquid possessing pungent odor and yielding an irritating vapor. Molecular weight 74; specific gravity 0.718 at 15°C.; boiling point 34.5°C.; specific gravity of vapor 2.6 (air equals 1). U.S.P. preparation contains alcohol (up to 3.5%).

Chemical—Does not react with alkalis. Reacts with sulphuric acid to form ethyl sulphate; with hydriodic acid to form alcohol and ethyl iodide.

Impurities of Manufacture—Alcohol, mercaptans, sulphuric acid, sulphur dioxide, ethyl esters, sulphurous acid, acetaldehyde and ether peroxide.

Impurities of Decomposition—Forms ether peroxides $[(C_2H_5)_2O]_2$, which act on the alcohol to form acetaldehyde. Oxidation of ether favored by air, moisture and light; retarded by copper, iron, mercury and zinc but not tin. Organic acids form later from aldehydes. Impurities prolong induction period. Not fatally toxic. Peroxides are unstable; may cause spontaneous combustion and contribute to explosion hazard.

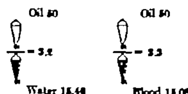
Storage—Sealed in metal containers coated inside with copper, iron or other metal which combines with oxygen; oxidation thereby retarded due to preferential absorption of oxygen by the metal. Oxidizes rapidly in open containers, in air, or when heated in the presence of oxygen.

Stability in Absorber—Not altered by soda lime or barium-lime mixtures.

Concentration—For analgesia less than 1% by volume in inhaled mixture. For anesthesia average 3.5% to 4.5% by volume. To cause respiratory failure 6.7% to 8%. Higher concentrations necessary during induction to saturate blood quickly. Possesses wide margin of safety. Respiratory failure precedes circulatory failure. Probability of resuscitation good in event of respiratory failure.

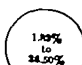
Induction—Prolonged, particularly second stage. Due to irritating qualities, high air blood ratio and moderate solubility in all tissues. Water solubility greater than is case with other common inhalation anesthetic agents.

Solubility—λ at 37°C.

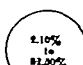


Inflammability—Flash point below 20°F. Ignition temperature 304° in air; in oxygen 182°C. 1 pound with air gives 277 cubic feet of inflammable mixture at 60°F. at standard pressure.

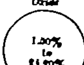
With Air

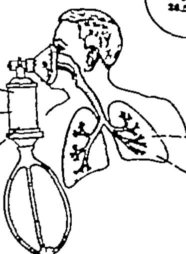


With Oxygen



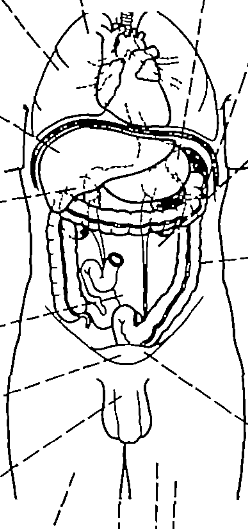
With Nitrous Oxide





Elimination—Not altered within the body; 85% to 90% of a given dose is eliminated through lungs; remainder through skin, urine or with other body fluids. Rate of desaturation depends upon depth and duration of anesthesia, amount of lipoid tissue and blood supply to tissues. Desaturation is slow, requiring many hours. Slow desaturation result of high blood solubility coefficient and moderate degree of solubility in "watery" tissues.

Diffusion—Passes rapidly through alveolar membranes. Diffuses from isolated lung lobule with occluded bronchus with circulation intact in 1 to 3 minutes (air = 18 hours).



Lymphatics—Absorption increased through peritoneal cavity particularly diaphragmatic portion. Enhanced by increased respiratory activity. Purulent material in peritonitis may be rapidly absorbed.

Adrenal—Sympathetic stimulation causes depletion of epinephrine content of gland.

Liver—Function decreased (Bromsulphalein dye test) returns to normal in 24 hours. Bile secretion decreased. Activity of reticulo-endothelial cells depressed. Glycogen content decreased rapidly (80%) in first hour then gradually decreased. Urea formation unaffected. No histological changes characteristic of drug.

Kidney—Oliguria in stage III, possibly due to release of anti-diuretic hormone from pituitary. Compensatory polyuria follows during recovery. Renal function further impaired in nephritis, nephrosis or other renal insufficiencies. No histological changes characteristic of drug.

Ureters—Stimulation of contractions during light anesthesia.

Bladder—Contracts at onset of stage III. Stretch reflex disappears causing atony of bladder and urinary retention. Reflexes may cause atony to persist in post anesthetic period.

Genitalia—No significant effects. Cholesterol content of testes reduced.

Body Temperature—Decreased due to decreased metabolic rate, depression of temperature regulating center and heat loss through skin due to dilatation of vessels.

Skin—Temperature increased due to dilatation of peripheral vessels. Sweating common particularly with anoxia or in warm environment. Blistering and burns may occur from local application under pressure.

Spleen—Constricted if structure is normal; blood flow unchanged. Causes erythrocytes to pass into systemic circulation.

Stomach—Swallowed vapors cause vomiting by irritation of mucous membranes. Movements decreased; emptying time decreased 50%. Gastric secretion decreased; acidity decreased. Muscle relaxed, causing dilatation 15 minutes to 1 hour after anesthesia.

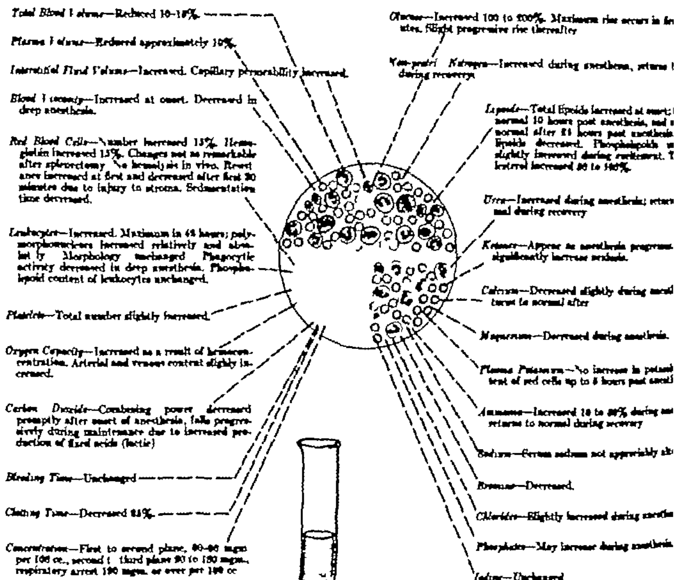
Pancreas—Insulin production decreased. Blood amylase increased 75–100%. Prevents or inhibits the action of insulin.

Intestines—Decreased peristalsis and secretions due to sympathetic stimulation and smooth muscle depression. Vessels dilated with loss of muscle tone. Peristalsis exaggerated on recovery. Mobility remains abnormal up to 48 hours. Colon becomes spastic 4 or 5 hours after recovery causing gas to accumulate in small bowel and cramps in post-operative period.

Uterus—Movements decreased. Intra-uterine pressure decreased. Relaxation complete in deep anesthesia. Drug passes through placenta. Arterial oxygen normal in fetus.

Muscles—Relaxation of skeletal muscles satisfactory. Glycogen content partly reduced. Lactic acid increased. Possesses curare-like action at end plates. Marked additive action with curare and tubocurarine.

Peripheral Nerves—Direct excitability not affected when central nervous system is depressed. Direct application depresses activity and conduction.



URINE

Output decreased during anesthesia. Phosphates increased up to 400%, albumin present in 30% of cases post anesthesia, ketones appear after anesthesia has been maintained for some time or post-operatively. Nitrogen output increased after anesthesia for 24 hours decreased during anesthesia.

USES

1. For all types of surgery particularly when relaxation of muscles is required.
2. For an additive effect with mildly potent agents.
3. As complemental agent to basal narcosis obtained with avertin, barbiturates and other non-volatile agents.
4. As an analgesic (rectally).
5. As an antispasmodic for rectal or intravenous use

CONTRAINDICATIONS

1. Presence of acute respiratory infection
2. Presence of chronic respiratory infection
3. Acidosis from any cause
4. Presence of severe hepatic or renal insufficiency or injury
5. Surgery requiring use of cautery
6. Shock from trauma or hemorrhage.
7. History of convulsions in previous anesthesias.

DISADVANTAGES

1. Period of induction prolonged, unpleasant and often accom
by excitement.
2. Recovery is slow (saturation and desaturation requires consid
time)
3. Inflammable
4. Irritating to respiratory passages, causing excessive salivatio
cous secretion and spasm.
5. Disturbs important metabolic functions.
6. Nausea and vomiting frequent post-operatively
7. Convulsions may occur in rare cases.

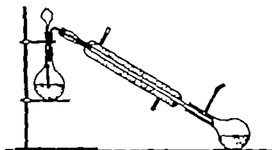
ADVANTAGES

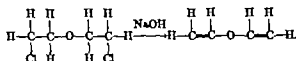
1. It is sufficiently potent for all forms of major surgery
2. It possesses a wide margin of safety
3. It is not a circulatory depressant at level of anesthesia usual
ployed for surgery
4. It tends to stimulate respiratory movements at level of anest
used for surgery
5. It is stable and easily preserved.
6. It is relatively inexpensive
7. May be administered with a minimum of equipment if necess
8. It allows use of air as a diluent and source of oxygen becaus
concentration required for anesthesia is low
9. Safest of the volatile agents in the hands of inexperienced ind
uals.

DIVINYL OXIDE (VINETHENE)

HISTORY—Apparently first prepared by F. W. Semmler in 1887 in Germany. First successful synthesis by William Ruigh in 1931. Anesthetic properties described by Chauncey Leake and M. Y. Chen in 1930 in United States. Further reports by Goldschmidt and Ravdin in 1933.

PREPARATION—Fusion of BB dichlor-ether with potassium hydroxide with ammonia as catalyst.





PROPERTIES

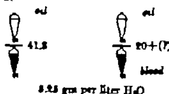
Physical—Highly volatile, clear limpid fluid, possessing an ethereal, non-pungent odor which yields a non-irritating vapor. Molecular weight 70; specific gravity 0.77 at 20°C.; boiling point 28.3°C. vapor specific gravity 2.2 (air equals 1).

Chemical—Unstable: decomposed by light, heat, air. Forms various peroxides, formaldehyde and acetic aldehyde which polymerize to resins. Also forms formic acid and acetic acid. Decomposition inhibited by ammonia and amines. Also known as vinyl oxide, divinyl ether, vinethene.

Impurities of Manufacture—Aldehydes, chlorethers, dioxane, ethylene oxide, acetic and formic acids and peroxides.

Storage—In dark, tightly-sealed bottle with an amine as anti-catalyst (Merck's "Vinethene" contains divinyl oxide, 4% absolute alcohol to prevent freezing of exhaled water vapor on mask, and .01% phenyl-alpha naphthylamine which acts as a stabilizer in preventing polymerization). Stabilizer confers fluorescent tinge to product. Opened bottle should be discarded 10 days. Decomposes slowly (two years?) in container. Should be discarded after date of expiration on label.

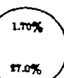
Solubility at 37.5°C.



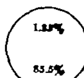
3.25 gm per liter H_2O

Inflammability—Highly explosive when vaporized with air or oxygen. Flash point below 24°F. One pound with air yields 318 cubic feet of explosive mixture at 60°F and at atmospheric pressure. Ignition temperature 680° in air; 681 in oxygen.

With Air



With Oxygen



With Nitrous Oxide



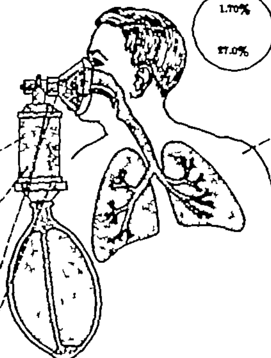
ADMINISTRATION

Open, semi-open or closed techniques may be used. Even anesthesia best obtained by open drop method. May be combined with nitrous oxide in semi-closed system.

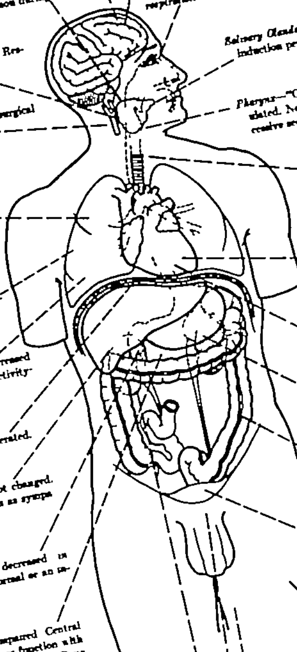
Induction—Rapid. Unconsciousness occurs in one or two minutes. Pleasant without excitement.

Effective Inspired Concentrations—Analgesia, approximately 0.5%; unconsciousness 2 to 4%. Anesthesia 4%; respiratory arrest 10 to 12%.

Stability in Absorber—Not altered by alkaline carbon dioxide absorbents.



Elimination—Not altered in the body. Major part eliminated through lungs. Recovery occurs in three to five minutes. Small amount eliminated through urine and other body secretions. Major portion eliminated within short period. Complete body desaturation slow because drug is lipophilic. Post anesthetic somnolence does not occur.


Cortex—Depressed. All planes of anesthesia obtained. Convulsions may occur from stimulation of central nervous system (subcortical centers) Minimized or prevented by premedication with morphine.
Intracranial Pressure—No remarkable or significant changes. Postanesthetic headache may follow
Eyes—Lid reflex disappears in first plane. Pupillary reflex to light remains active horizontal nystagmus eyeballs rotat even in third plane ane thesia. Movements not reliable for judging anesthesia. *Judge depth* respiration not eye signs.
Vomiting Center—Not stimulated. Nausea not common during recovery
Salivary Glands—Frequently copious secretions during induction period controlled by atropine.
Respiratory Center—Depressed only in plane 4 Respiration fails before circulation.
Pharynx—"Gag" reflex abolished. Mucous glands sti ulated. No laryngeal spasm. Occasionally causes e cessive secretion of mucus.
Vasomotor Center—No appreciable effect during surgical anesthesia.
Larynx—Laryngeal reflex abolish deep anesthesia. Spasm and pho may occur from excessive mucu
Lungs—Non-irritating to epithelial lining At onset respirations rapid and shallow respiration ceases before circulation fails. Minute volume exchange increased at onset and in light anesthesia; decreased in deeper planes.
Heart—No notable cardiac effec rat slightly increased or d EKG not changed. N effect automaticity Arrhythmias w Does not sensitize heart to e
Bronchi—Dilated. Bronchospasm uncommon.
Blood Pressure—Not changed o creased in deep anesthesia.
Metabolism—Oxygen consumption increased at onset due to increased muscle activity decreased during maintenance
Stomach—Gastric tone increased. Emptying time decreased 7%.
Diaphragm—Movements not exaggerated.
Intestines—Decreased muscular tone of small bowel. Movements inhibited in vivo; de creased in deep anesthesia. Data on effect on colon lacking.
Adrenal—Epinephrine content not changed. Drug behaves in some respects as sympathomimetic substance.
Uterus—Frequency of contractions not fected in light anesthesia and small drug passes to fetus.
Gallbladder—Bile secretion decreased in amount with return to normal or an increase after anesthesia.
Skeletal Muscles—Relaxation of abdominal muscles not satisfac laparotomies muscles of extremities relaxed for minor surgery
Liver—Dye excretion not impaired Central necrosis and decreased liver function with anoxia on prolonged or repeated use. Drug contraindicated in liver disease.
Skin—Sweating minimal No cyanosis. Possibility of burns as pressure and direct contact of agent on cutaneous areas.
Kidney—No evidence of impaired function after brief periods of use Impaired urea clearance after prolonged or repeated use
Sphincters—Relaxed in lower planes of anesthesia.

BLOOD

Oxygen Capacity—Unchanged.

Oxygen Content—Unchanged in arterial system.

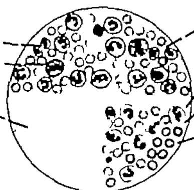
Carbon Dioxide Combining Power—Slightly elevated or unchanged.

Glucose—Unchanged.

Clotting Time—Unchanged.

Bleeding Time—Unchanged.

Blood Concentration—Average 11 mgm. per 100 cc. for 1st plane; average 16 mgm. for 2nd plane; 28 for 3rd plane and 68 mgm. for respiratory failure.



PATHOLOGY

Central necrosis of liver lobule in animal experiments in prolonged anesthesia or when administered with anoxia. No definite evidence of any similar effect on man.

URINE

No significant changes. Urea clearance impaired in prolonged anesthesias or in repeated administrations.



USES

(1) For analgesia for minor operations (exodontia, obstetrics, etc.) of short duration (less than 10 minutes).
(2) For anesthesia for brief surgical procedures not requiring relaxation.
(3) As a preliminary to open drop ether anesthesia to shorten second stage.
(4) As complement to nitrous oxide or ethylene anesthesia.
(5) In combination with ethyl ether.

DISADVANTAGES

(1) Relatively expensive (compared to ether).
(2) Inflammable.
(3) Not as stable chemically as other volatile agents.
(4) Possibility of convulsions, particularly in unpremedicated subjects.
(5) Muscle relaxation unsatisfactory.
(6) Eye signs not reliable guide to anesthesia.
(7) Possibility of hepatic or renal damage in repeated prolonged use.
(8) Excess salivation occasionally encountered.
(9) Odor objectionable at first.
(10) Post-anesthetic headache occasionally seen.
(11) Highly volatile at room temperature.
(12) Chances of resuscitation less than with ether in event of overdosage.
(13) Not satisfactory in closed system.

CONVULSIONS

Features

(1) Occur during induction.
(2) Occur in unpremedicated subjects.
(3) Due to stimulation of spinal and subcortical motor centers.
(4) Disappear when agent is discontinued.

CONTRAINDICATIONS

(1) Operations requiring muscle relaxation.
(2) Operations lasting more than 15–20 minutes.
(3) The presence of hepatic, renal disease or tendency to "convulsive states."
(4) The presence of anoxia.
(5) The presence of cautery or other source of ignition.

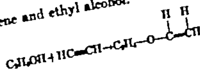
ADVANTAGES

(1) Rapid, pleasant induction.
(2) Rapid recovery.
(3) Excitement rare.
(4) Non-irritating to respiratory tract.
(5) Nausea and vomiting uncommon.
(6) Minimal equipment necessary for administration.
(7) Does not depress respiration.
(8) Does not affect circulation.
(9) May be inhaled directly without unpleasantness, spasm or coughing.
(10) Respiration ceases before circulation in overdosage.
(11) Yields all planes of anesthesia.
(12) May be combined with ether or nitrous oxide.
(13) Does not notably interfere with important physiological functions.
(14) Useful for emergency room surgery.

VINYL ETHYL ETHER (VINAMAR)

HISTORY—First studied by Leake in 4 mice (U.S.) in 1930 who obtained specimen from Fraenkel (Vienn investigation by J C Krantz and co-workers in 1947 Intermediate between ethyl and vinyl ether S found it less potent than ether in frogs.

PREPARATION—By interaction of acetylene and ethyl alcohol.



$$C_2H_5OH + HC{\equiv}CH \rightarrow C_2H_5{-}O{-}\overset{H}{\overset{|}{C}}{=}\overset{H}{\overset{|}{C}}H$$

PROPERTIES

Physical—Clear colorless, mobile liquid. Pungent odor resembles ethyl ether M W 72.10 B.P 35.8°C.; S.G 0.75 at 20°C. S G vapor (air=1) 2.49 Solubility: 0.8 ml. per 100 ml. in water Vapor tension (22°C.) 463 mm. Hg.

Chemical—A mixed ether Hybrid between ethyl and vinyl ether

Stability—Unstable Polymerizes to resins, oxides, aldehydes and peroxides. Stabilized with 0.01% alphaphenylnapthylamine Three per cent alcohol added to prevent freezing of water vapor on mask. May hydrolyze to acetylene and alcohol in acid solution.

Impurities—Peroxides, aldehydes, resins.

Storage—In brown bottles with stabilizer of 0.01% alphaphenylnapthylamine

Stability in Canister—Stable in presence of alkali in CO_2 absorbers.

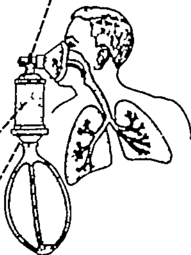
Administration—Unpleasant odor Induction rapid. (1) Usually by open drop, (2) by semi-closed system with air oxygen or nitrous oxide, (3) by closed system.

Solubility—Oil/water coefficient 44 at 22°C.

Flammability—Lower limit 2.1% in air

Elimination—Unchanged. Not hydrolyzed in the body

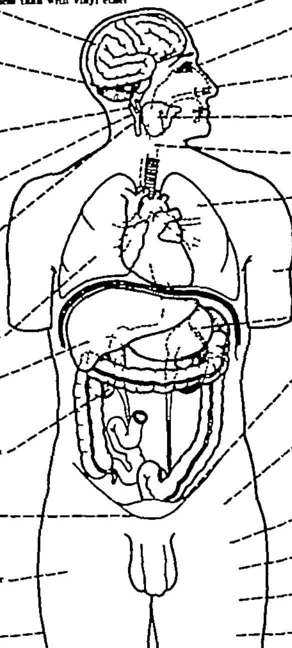
Induction—Smooth, rapid, no breathholding Longer t ether shorter than with ethyl ether

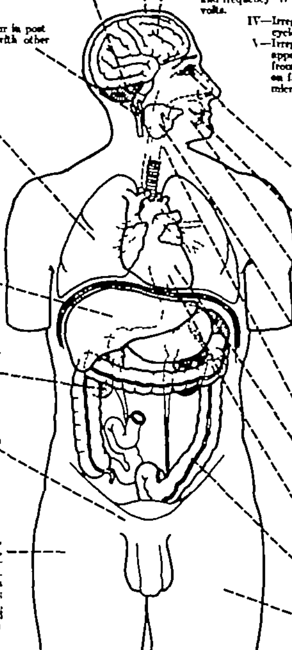


USES
(1) To fortify nitrous oxide.
(2) As an induction agent for ether
(3) For surgical procedures not requiring
(4) As an analgesic.

DISADVANTAGES
(1) Unpleasant odor
(2) Neuromuscular phenomenon.
(3) Salivation.
(4) Nausea and vomiting.
(5) Muscle relaxation poor
(6) Flammable—fire hazard.
(7) Convulsions may occur (as with vinyl ether)
(8) May cause headache in certain patients.

ADVANTAGES
(1) Induction more rapid than ethyl ether less than vinyl ether
(2) Emergence more rapid than ethyl ether less than vinyl ether
(3) Lower volatility than vinyl ether
(4) Margin between respiratory arrest and circulatory arrest wide
(5) Overdosage phenomenon reversed easily
(6) May be administered by open method.
(7) Quickly eliminated, suitable for ambulatory patients.


Cortex—Poses excess cortical activity characteristic of compounds with vinyl radical. Neuromuscular phenomena less than with vinyl ether. May cause headache.
Medulla—*Respiratory Center*—Depressed. Respiration ceases before circulation.
Vasomotor Center—Depressed in deep anesthesia.
Vagus Center—Increased activity absent.
Vomiting Center—Nausea and vomiting common but less than with ethyl ether and more than with vinyl ether
Lungs—Stimulates respiratory activity as does ethyl ether but not to same degree. More than with vinyl ether. No pulmonary irritation.
Liver—Some retention of B.S.P.
Kidney—No significant changes in function postoperatively
Sphincters—Not relaxed.
Muscles—Relaxation inadequate for major surgery. Requires supplementation.
Skin—May cause burns if contacts.
Intracranial Pressure—No clinical evidence of increased pressure
Eye—May cause irritation. Signs of anesthesia similar to those of vinyl ether. Roving eyeballs become fixed in Stage IV
Mucous Membranes—Slight irritation. Greater than vinyl ether; less than ethyl ether
Salivary Glands—Marked salivary secretions without atropine.
Larynx—Spasm possible but not common unless secretions are excessive.
Heart—Light anesthesia causes no significant changes. Deep anesthesia causes tachycardia, ventricular and auricular extrasystoles in 1 of 4 or 5 patients.
Blood Pressure—Tends to fall in deep anesthesia. Unchanged in light or moderate depth.
Gastro-intestinal—Nausea and vomiting less frequent than with ethyl ether; more frequent than with vinyl ether
Uterus—Passes placental barrier. Does not relax uterus. Inhibits uterine activity in deep anesthesia.
Muscles—Relaxation not adequate for major surgery. Not as great as with ethyl ether. Greater than with vinyl ether. Running movements and convulsions may occur but less frequent than with vinyl ether
Reflexes—Superficial reflexes obtunded.
Blood—Urea not elevated.
CO_2 *Combining Power*—Not changed.
Clotting Time—Prolonged 10-15%. Not of clinical significance.


Intracranial Pressure—No clinical evidence of increased pressure.
Respiratory Center—Not depressed during analgesia or light anesthesia. Depression occurs as anesthesia deepens into lower planes.
Vomiting Center—Nausea and vomiting occur in post operative patient but no greater than with other ethers.
Lungs—Not irritating to alveolar membranes. Minute volume exchange increased but not the same degree as with ethyl ether. Tachypnea develops as anesthesia deepens. In spite of increased rate decreased tidal volume occurs. Tachypnea masked by narcotic premedicants. Respiratory acidosis develops as anesthesia deepens.
Liver—No change in bromsulphthalein excretion. Thymol turbidity unchanged. No pathologic changes.
Kidney—No pathologic changes. No significant changes in urea clearance.
Sphincters—Not relaxed. Muscle relaxation poor.
Blood—Glucose not changed. Urea nitrogen, CO_2 combining power unchanged. R.B.C., W.B.C. not changed in number or morphology. Bleeding and clotting time unchanged. Concentration in venous blood—analgesia 17 mgm. Plane 1 up to 20 mgm. per 100 cc; plane 2—25 mgm; plane 3—28 mgm., plane 4—38 mgm. apnea—50 mgm. Blood level falls from 22 to 4 mgm. in 4 minutes. More carried by blood cells than plasma.
Cortex—Cumulative effects not observed. E.E.G. levels similar to ether. Six patterns
I—Resting alpha rhythm replaced by activity of 15–25 cycles per second—Voltage 25–50 microvolts.
II—Waves of slower frequency—4–6 cycles voltage up to 50 m.v. appear as spindles superimposed on previous fast activity—Last 6–8 sec.
III—Fast activity pattern ceases. Dominant waves increase in voltage and frequency. Waves=3–5 cycles per second at 100–300 microvolts.
IV—Irregular slow waves at 100–300 microvolts and 2–4 cycles per second. No tendency to repetition.
V—Irregular slow high voltage waves of long duration appear at 1–8 seconds with a 1–2 second spread and from 100–175 microvolts. These are superimposed on fast waves of 2–5 cycles per second with 25–75 microvolt amplitude.
VI—Slow wave frequency decreases to 1 every 12 seconds. Superimposed waves of 3–5 cycles per second at 25–50 microvolts which appear only between dominant waves.
Eyes—Signs similar to vinyl ether
Mucous Membranes—Not irritated. Mucous formation occurs but less than with ethyl ether
Pharynx—Pharyngeal reflex abolished. Airways tolerated.
Salivary Glands—Salivation and mucous secretions minimal. Less than ethyl ether
Larynx—Spasm uncommon.
Heart—Increase in pulse rate. Does not sensitize heart to epinephrine. Arrhythmias uncommon.
Blood Pressure—Hypotension in deep anesthesia. No depression in light anesthesia.
Gastro-intestinal—Nausea and vomiting occur
Muscles—Muscle relaxation not adequate for major surgery. Requires supplementation. Jaw muscles tend to remain rigid.

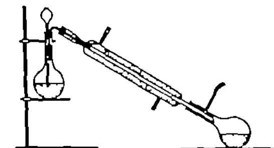
LESS COMMON ETHERS

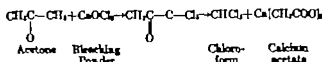
	Di Methyl Ether	Propyl-Ethyl Ether	Propyl Methyl Ether	Isopropyl Methyl Ether	Propethylene	Cyclopropyl Methyl Ether	Cyclopropyl Ethyl Ether	Cyclopropyl Vinyl Ether
History	Introduced by Richardson in 1867 in man and animals.	First studied and used by W. E. Brown, Toronto, 1930.	J. C. Krantz studied it effects on animals in 1946 (metopryl)	Also known as Isopryl. J. C. Krantz first studied it.	Studied by Davis and Krantz—1944.	Krantz and co-workers prepared and reported its use on man in 1930 as cyprome.	Introduced by Krantz and co-workers in 1934 on man as cypreth	
Properties	Colorless gas with unpleasant odor Soluble 37 vols. in 1 H_2O.	Clear colorless liquid with ethereal odor B.P. 63.6°C. S.G. 75.	Isomer of ethyl ether Volatile colorless liquid with sweet odor B.P. 39°C. Oil water ratio 30. S.G. 0.736 (14°C.)	An isomer of ethyl ether Oil water ratio 2 at 37°C. Unsaturation tends to [illegible]	Isopropenyl vinyl ether. Clear colorless mobile liquid. B.P. 55°C. Odor somewhat like cyclopropane.	Colorless liquid. B.P. 44°C. S.G. 0.78 at 25°C. 8.8 cc. dissolves in 100 cc. H_2O. Oil water ratio 6.7 at 37°C.	Oil water ratio 4.1. B.P. 68. Clear volatile colorless liquid with ethereal odor 2.2 cc. Dissolves in 100° water at 20°	Cypre… ether. 67°C. ratio…
Potency	Less potent than ethyl ether.	Approximately twice that of ethyl ether	30 to 40% more potent than ethyl ether	25% less potent than ethyl ether	Approximately four times more potent than ethyl ether	More than ethyl ether	More potent than ethyl ether Approximates that of chloroform.	Less potent than vinyl ether.
Inflammability	Highly inflammable.	Approximately same as ethyl ether	Same as ethyl ether	Same as ethyl ether	Approximately same as ethyl ether	Similar to other ethers.	Inflammable.	Inflammable.
Concentration	Unconsciousness 10%. Anesthesia 50 to 60%. Resp. failure 85%.	4–5% yields surgical anesthesia.	Anesthesia 0.84 cc Kgm. Resp failure 2.10 cc. Kgm.	Anesthesia 0.98 cc. Kgm. Resp. failure 1.84 cc. Kgm.	Less than ethyl ether	Anesthesia 0.64 cc. Kgm. Respiratory failure 1.46 cc Kgm.	Anesthesia 0.90 cc. Kgm. Respiratory failure 1.88.	0.36 cc. per Kgm.
Induction	Induction slow and difficult irritating	Slower than with ethyl ether Not unpleasant.	Less irritating than ethyl ether More rapid effect. Shorter second stage.	Rapid induction and ve y Faster than with ethyl ether	Rapid recovery and induction. Similar to cyclopropane or vinyl ether	Same or slightly shorter than with ethyl ether	[illegible] with difficulty	
Elimination	Eliminated through lungs unchanged.	Slowly unchanged like ethyl ether	Not changed in body More rapid than with ethyl ether	Probably unchanged.	Unchanged through lungs.	Unchanged in body Similar to ethyl ether	Unchanged through lungs.	Unchan…
Circulatory effects	No significant effects.	No significant effects.	No significant changes. B.P. falls in deep anesthesia.	No significant disturbances or effects.	Increases pulse rate. Does not cause arrythmias.	No significant changes in blood pressure.	No significant effects. Does not cause arrythmias.	
Respiratory effects	Irritating. Stimulates production of mucous.	Respiratory failure occurs before circulatory	Quieter respirations than with ethyl ether Less irritating than ethyl ether	Irritating	Some increase in respiratory rate. Less irritating to respiratory tract than ether	Stimulated. Some laryngeal spasm. More irritating than ethyl ether.	More irritating than ethyl ether or cyprome. Causes marked spasm of larynx. May cause pulmonary edema.	More irritating than vinyl ether
Metabolic effects	Not described		Liver function depressed similarly to ethyl ether	No functional liver changes or damage.				
Muscle relaxation	Running movements common.	Comparable to ethyl ether	Similar to ethyl ether in some phases.		Comparable to ethyl ether	Comparable to ethyl ether.	Compares favorably with ethyl ether.	
Renal function	Not described.		Oliguria during and after anesthesia similar to ethyl ether		No significant effects.	No change.	Not significantly altered.	
Method of administration	Closed or semi-closed method	By open or closed methods.	Open drop or closed system Pleasanter to inhale than ethyl ether	By open or closed methods.	Open, semi-open, semi-closed or closed method may be used.	Open drop or by closed system.	Open drop or closed system.	Closed o… Not … only
Stability	Stable.	Stable.	Chemically stable. Decomposed by heat, light and air		May contain traces of acetone as impurity. Hydrolyzed to acetone by acids.	Stable under ordinary conditions.	Chemically stable.	

CHLOROFORM

HISTORY—Prepared by Liebig, Soubeiran and Guthrie independently in 1831 Anesthetic properties discovered by Flourens in 1847 on animals and by Simpson in 1848 on man at the suggestion of McWaldie and Duncan at Edinburgh

PREPARATION—Most common method is to chlorinate ethyl alcohol or acetone in the presence of alkali. Chlorine and sodium hydroxide or bleaching powder may be used





$$CH_3C(=O)-CH_3 + CaOCl_2 \rightarrow CH_3C(=O)-C-Cl_3 \rightarrow CHCl_3 + Ca(CH_3COO)_2$$

PROPERTIES



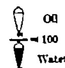
Physical—A clear limpid heavy fluid possessing sweet, pleasant odor somewhat irritating Molecular weight 119.3 specific gravity of vapor 4.12 (air equals 1); boiling point 61°C., melting point −63°C. One cc. dissolves in 210 cc H_2O at 20°C.

Chemical—Decomposed by alkalis to formates. Easily oxidized to phosgene when heated Chemical name is *trichloromethane*

Impurities—Aldehydes, ketones, ethyl alcohol, esters, phosgene and formates. Formation of phosgene counteracted by addition of 1% alcohol which combines to form ethyl carbonate and ethyl chloride

Storage—In dark, tight-stoppered bottle with 1% alcohol, protected from light, heat and air Included in U.S.P

Solubility—High lipoid, low water solubility Oil-water coefficient 100 at 20°C. Concentration in body fluids varies with nature of the body fluid and tension of the vapor inhaled. Concentration greater in red cells than in plasma air/blood distribution at 37°C. = 10.3



Inflammability—Vapor non-inflammable and does not support combustion Oxidized in presence of flame to *phosgene*, which is irritating if inhaled.

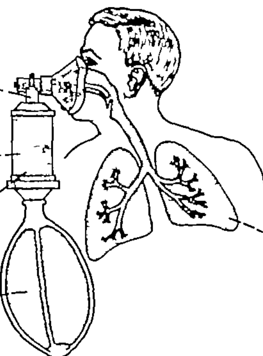
ADMINISTRATION

By the open drop or closed techniques. High O_2 in closed system protects against liver damage May be insufflated or used in semi-closed system with nitrous oxide Also used in combination with other drugs such as ether and alcohol (A.C.E. mixture)

Effective Inspired Concentrations—Analgesia 0.25%–0.75% light anesthesia 0.75%–1.25%, deep anesthesia 1.25–1.65% respiratory arrest 2% in inhaled mixture As much as 4% may be needed during induction.

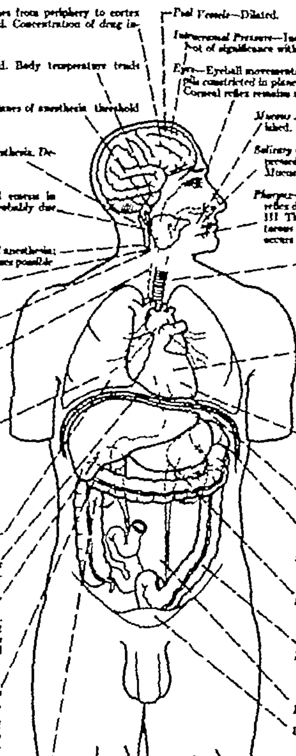
Stability in Absorber—Not entirely stable Small amount of formic acid forms by interaction with alkali. Formic acid reacts with the alkali to form sodium formate (harmless)

Induction—Rapid, not unpleasant and not accompanied by discomfort and unpleasantness noted with ether



Non-flammable

Elimination—Not altered within the body Major portion eliminated through lungs. Approximately 80% eliminated five to seven minutes after conclusion of anesthesia. Traces may appear in exhalations for as long as 24 hrs. Traces also appear in urine, sweat, milk and excreta of gastro-intestinal tract. Possibility of small amount being altered and causing liver damage not excluded but not proved.



Brain—Pathways carrying sensory impulses from periphery to cortex interrupted. Brain metabolism depressed. Concentration of drug increased in brain before other tissues.

Temperature Regulating Center—Depressed. Body temperature tends towards environmental temperature

Respiratory Center—Depressed in deeper planes of anesthesia threshold to CO_2 raised.

Vasomotor Center—Not affected in light anesthesia. Depressed in deeper planes of anesthesia.

Vomiting Center—Depressed. Nausea and emesis in post-anesthetic period common. Most probably due to central effect.

Vagus Center—Depressed in deeper planes of anesthesia; active in light anesthesia. Vago-vagal reflexes possible

Carotid Body—Remains active

Carotid Sinus—Depressed in deeper planes of anesthesia.

Thyroid—No notable effect. Repeated administration of thyroxin decreases resistance to drug

…nia—Respiration increased in rate and depth during induction and in light anesthesia. Minute volume exchange decreased in deeper planes of anesthesia. Hering-Breuer reflex remains active. Bronchial muscle relaxed. Secretions increased. No change in alveolar membrane

…tabolism—Decreased

…phragm—No notable change in upper planes of anesthesia. Movements decreased in deep anesthesia

…renal—Depletion of epinephrine content. Release of epinephrine during excitement and induction period thought to induce ventricular fibrillation in face of increased cardiac irritability

…er—Function temporarily impaired as measured by bromsulphalein retention, galactose and fructose tolerance tests. Glycogen three-fourths depleted in first half hour less rapidly afterward. Bile formation decreased. Urea formation normal. Prothrombin time prolonged. Bile pigments increased in blood. Severity and duration of dysfunction varies with depth of anesthesia. Hepatitis may follow

…ney—Oliguria during anesthesia, followed by polyuria during recovery possibly due to release of anti diuretic hormone. Albumin appears in one-third of cases. May aggravate existing renal disease

Pial Vessels—Dilated.

Intracranial Pressure—Increased slightly. Spinal Not of significance without anoxia or hypercaq

Eyes—Eyeball movements remain active in plane pils constricted in planes 1 to 3, dilated during Corneal reflex remains active into plane 3. Lig

Mucous Membranes—Irritated. C lished. Mucus secretion increa

Salivary Glands—Stimulated at pressed during anesthesia, a Mucus secretion increased.

Pharynx—Mucosa not irritated reflex depressed. Pharyngeal a III. Thick mucus secreted if torous respiration due to spasm occurs if anoxia is present.

Larynx—Laryngea concentrations. lished in plane Vago-cardiac ref Irritation of resp

Heart—Myocardiu planes of anesth cient to cause r also cause cardia sudden death. Al tissues to epinep mine. Ventricula brillation follows Procaine reduces output decreased

Blood Pressure—Littl planes. Falls, due t pression of vasomoto dilation in deeper plane

Venous Pressure—Slig planes. Decreased le increase in deep anes tation supervenes.

Spleen—Constricted. I truded into blood st hemoconcentration.

Stomach—Movements d Tone decreased. Di Slowly recovers after activity inhibited or

Intestines—Movements lished. Secretory activ lished. Recovery occur Movements exaggerat

Pancreas—Blood lipase

Uterus—Contractions d anesthesia abolished in deep anesthesia. D Pregnancy does not damage

Skin—Vessels dilated. Temperature elevated. Irritat

Skeletal Muscles—Slight reduction in tonus in plane tion in planes 2 and 3. Complete relaxation in pla

Body Temperature—Decreased 1 to 4°F due to dep lating center peripheral vascular dilatation and

Total Blood Volume—Decreased. Varies with duration and depth of anesthesia.

Red Blood Cells—Increased in number. Immediate decrease in fragility due to damage to stroma. Sedimentation rate decreased. No hemolysis occurs in vivo. Hemoglobin increased.

Leukocytes—Increased in post-anesthetic period with return to normal within 48 hours. Maximal within 24 hours. Polymorphonuclear cells increased relatively and absolutely. Morphology unchanged. Decrease in phagocytosis.

Platelets—Unchanged.

Clotting Time—Decreased after one-half hour. Prothrombin time prolonged.

Oxygen Capacity and Content—Capacity increased. Blood specific gravity increased. Viscosity increased. Oxygen content reduced in deep anesthesia.

Total Carbon Dioxide—Increased.

Carbon Dioxide Combining Power—Decreased shortly after onset of anesthesia. pH decreased. Gradual return to normal after recovery.

Concentration—85% in red cells (more than lipoid content allows—possible combination with protein).

Concentration—20 to 30 mgm. per 100 cc. of blood. 30 to 40 depressant. 40 to 60 fatal.

Glucose—Increased up to 200%.

Lipoids—Slight increase in total lipoids. Considerable sustained increase if hepatitis occurs. Unsaturated fatty acids and cholesterol fractions increased over neutral fats.

Lipase—Increased if hepatitis occurs.

Amino Acids—Increased if post-operative hepatitis occurs.

Non-protein Nitrogen—Normal in 24 hours. Increases *with return to normal during recovery.* Elevated if hepatitis occurs.

Urea—Increased during anesthesia. Decreased if post-operative hepatitis occurs.

Ammonia—Increased if post-operative hepatitis occurs.

Phosphates—Decreased during, but increased in recovery period.

Bile—Increased if hepatitis occurs. Slight increase otherwise.

Ketones—Appear during terminal phase of prolonged anesthesia.

Bromine—Decreased during anesthesia.

Iodine—Decreased during anesthesia.

URINE



Volume—Decreased during anesthesia. Anuria may occur.

Chlorides—Increase after anesthesia.

Phosphates—Decrease during and increase for a few hours after anesthesia.

Glucose—Not present.

Reducing Action—Drug which passes into urine may give false positive tests for sugar.

Nitrogen—Total nitrogen decreased during and increased after anesthesia.

Albumin—Present in one-third of cases.

Hepatitis with Liver Damage—Bile increases. Ammonia increases; amino acids increase; urea decreases.

Blood—May occur if hepatitis occurs.

PATHOLOGY

Cause—Prolonged administration over 30 to 60 minutes or administration while blood pressure is reduced may be followed by *hepatitis*. Starvation may predispose. Feeding glycogen, xanthines, amino acids and protein afford protective action. Anoxia enhances effects. Administration with oxygen decreases incidence. May be result of decomposition of part of chloroform to halogenated derivative in liver.

Symptoms—Those of acute toxic hepatitis. Fever. Jaundice, bleeding tendency, reduced liver function, bile and plasma fibrinogen, amino acids in urine, reduced serum prothrombin time, prolonged bleeding and clotting time. Increased serum bilirubin.



Changes in Liver—Cloudy swelling followed by necro[…] of cells in center of liver lobules surrounding cent[…] vein. Changes appear 6 to 10 hours after conclusion [of] anesthesia. Become maximal in 48 to 72 hours. L[…] becomes atrophic. Death may occur on 4th or 5th […] Regeneration follows survival. Fibrous […] cept in cases of chronic poisoning following repeat[…] ministration.

Changes in Other Organs—Fatty degeneration in tubules of kidney. Glomeruli not altered. Cloudy swelling of myocardium. Hemorrhages into gastro-intestinal tract due to hemorrhagic subserous areas throughout. Hemorrhagic areas in parenchyma of pancreas. Necrotic areas in placenta of pregnant females.

USES

(1) As an analgesic in obstetrics and minor surgical procedures.
(2) As a preliminary or induction agent for ether.
(3) For major surgery requiring relaxation.
(4) For use when cautery or electrosurgical unit are required.
(5) For securing extreme degrees of relaxation of uterus in obstetrics (Bandl's ring).

CONTRAINDICATIONS

(1) Cardiac diseases.
(2) Hypertension.
(3) Hypotension (shock).
(4) Diabetes mellitus, or acidosis from any cause.
(5) Hepatitis or liver dysfunction.
(6) Renal diseases.
(7) Acute respiratory infections.
(8) In emaciated, cachectic "toxic" anemic or acutely ill pati[…]
(9) In hands of the inexpert.

ADVANTAGES

(1) Yields excellent relaxation.
(2) Induction is rapid, not unpleasant and does not require use of a preliminary induction agent such as nitrous oxide or ethylene.
(3) *It is non-inflammable.*
(4) Very simple equipment may be used to administer it—mask and dropper bottle.
(5) Volatility is of such a degree that it may be used in tropical climates.
(6) Respiration is not unduly stimulated or depressed.
(7) Low concentration required for surgical anesthesia allows air to be used as vehicle and source of oxygen.
(8) Chemically stable and easily preserved.
(9) Inexpensive.

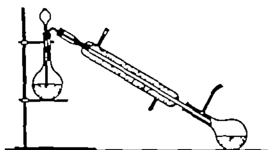
DISADVANTAGES

(1) Possesses a narrow margin of safety.
(2) Depresses myocardium. Concentration causing respirator[…] also causes serious cardiac failure.
(3) Sensitizes the automatic tissues of the heart, causing spo[…] arrythmias.
(4) Causes arrythmias, even ventricular fibrillation with e[…] and sympathomimetic amines.
(5) Hepatitis may follow in the post-operative period.
(6) Severe biochemical and metabolic disturbances follo[…]
(7) Flames, cautery sparks, etc. oxidize it to phosgene, [… dan]gerous if inhaled, causing pulmonary edema.
(8) Elimination is slow.
(9) Of questionable safety.
(10) Post-anesthetic nausea and vomiting very commo[…]
(11) Irritating to skin and mucous membranes.
(12) Not easily volatilized at ordinary room temperat[…]

TRICHLORETHYLENE

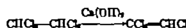
HISTORY—First described in 1864 Plessner discovered analgesic properties in 1917 Studied as an anesthetic by Dennis Jackson and co-workers (Cincinnati) in 1935 in U S and used in limited number of clinical cases. C. L. Hewer England revived interest in it in 1939 in search of a potent, non inflammable anesthetic

PREPARATION—Acetylene is chlorinated to form tetrachlor ethane which is boiled with lime.





$$CH \equiv CH + Cl_2 \longrightarrow CHCl_2—CHCl_2$$



$$CHCl_2—CHCl_2 \xrightarrow{Ca(OH)_2} CCl_2 = CHCl$$



PROPERTIES

Physical—Clear colorless fluid, possessing an odor somewhat similar but less pungent than chloroform. B.P 87°C. M.W 130—S.G 1.47 at 15°C. Vapor heavier than air (S.G 4.53)

Chemical—Stable under ordinary circumstances. Decomposed by light and heat and air Mixes with ether in any proportion. Compatible with nitrous oxide

IMPURITIES

Decomposed by oxidation to dichloracetyl chloride hydrochloric acid and phosgene Decomposition retarded by 0 01% thymol. Often colored with methylene blue to distinguish it from chloroform. Impurities detected by testing with Congo Red for the hydrochloric acid, silver nitrate for aldehydes and cadmium iodide and starch for free chlorine

SYNONYMS

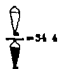
Trilene, chlorylene, westrosol.

STABILITY

Not stable in the presence of alkaline absorbents. Forms dichloroacetylene, which is explosive and phosgene. Both are toxic if inhaled. Heat accelerates decomposition of agent.

SOLUBILITY

Highly soluble in lipoids. Insoluble in water



=34 4



INFLAMMABILITY

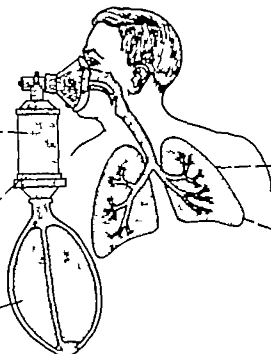
Not inflammable in concentrations below 10% with air or oxygen. Vapor mixed with pure oxygen may ignite above 66°F but not if mixed with air

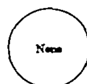
STORAGE

Packed in amber bottles to protect from light.

ADMINISTRATION

By inhalation using the open, semi-open insufflation or semi-closed techniques Cannot be used with soda lime or Baralyme in the closed technique Vaporizes slowly in open technique Best results are with semi-closed method using nitrous oxide and oxygen





Elimination—Unchanged through the lungs and other channels of excretion. Partial decomposition of small percentage of drug in body believed to occur

Induction—Pleasant and comparatively rapid. Longer than cyclopropane Non-irritating V porized with difficulty

Recovery—Rapid after brief administration of light anesthesia.

Concentrations—Analgesia—0 1-2% anesthesia—6 0-7.5%.

Cortex—Depressed. Has potent analgesic effect. Onset rapid. Causes amnesia. Depresses cortical potentials (see electroencephalogram.)

Vasomotor Center—Apparently not affected in moderate depths of anesthesia. Depressed in deep anesthesia.

Respiratory Center—Depressed in Stage III

Cough Center—Depressed.

Vomiting Center—Nausea and emesis in post-anesthetic period in 20% of cases. Uncommon when used for analgesia or with nitrous oxide.

Cranial Nerves—Vulnerable to by-products of deterioration. Soda lime slowly converts drug to dichloracetylene which causes bilateral anesthesia of Vth nerve, if inhaled. Complication more apt to occur in patient who follows one exhaling drug into closed system after periods of analgesia. Patient receiving drug not necessarily affected. Pure drug not specific for Vth nerve

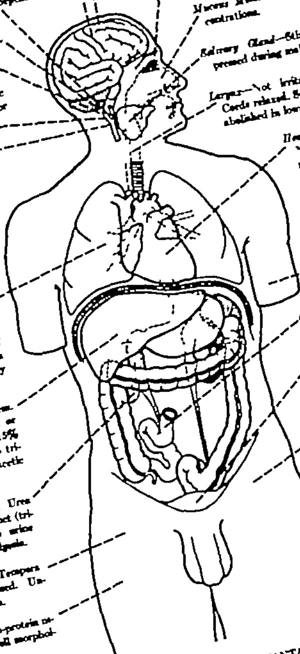
Lungs—Tachypnea frequent during anesthesia—rate may be as high as 60 to 100. Minute volume exchange may be reduced in spite of rapid rate due to sensitization of deflation receptors in alveoli. Tachypnea sign of deep anesthesia. Reflex obtunded by meperidine and other narcotics.

Liver—Impairs excretion of bromsulphalein. Histological changes follow prolonged or repeated use of drug. Detoxified up to 15% by conversion to chloral reduction to trichlorethanol and oxidation to trichloracetic acid.

Kidney—Renal clearances unchanged. Urea values unchanged. Oxidized biproduct (trichloracetic acid) eliminated into urine. Function not decreased during analgesia.

Body Temperature—Usually falls. Temperature regulating center depressed. Unchanged when used for analgesia.

Blood—No change in sugar or non-protein nitrogen. No changes in blood cell morphology



Intracranial Pressure—Not changed. Suitable for neurosurgery and ... N_2O. No changes with analgesia.

Eye—Movements of eyeballs persist into lower planes. Pupils do ... readily dilate in deep anesthesia.

Mucous Membranes—Not irritated by analgesi... centrations.

Salivary Gland—Stimulated during induct... pressed during maintenance.

Larynx—Not irritated in analgesic concentrations. Cords relaxed. Spasm not common. Laryngeal refle... abolished in lower planes.

Heart—Cardiotoxic. Less so if used wit... N_2O. Irregularities common. Arrhyth... mia caused by increased vagal ton... Later during first and second pl... ectopic foci in auricle and ventri... give way to ventricular tachycardia. Enhanced by epinephrine. No effect on coronary vessels.

Blood Pressure—No significant deviation during surgical anesthesia. Falls in deep anesthesia. Oozing negligible.

Colon—Absorbed from colonic mucosa wh... administered rectally

Uterus—Suitable as analgesic for obstet... Not inhibited during analgesia. ... passes into fetal circulation. No fe... pression if used for analgesia.

Muscles—Relaxation not always satisf... Activity marked during early pl... anesthesia.

Reflexes—Not completely obtunde... frequently moves when stimul... in deeper planes of anesthesia.

Skin—Dermatitis follows from ... repeated use on occasions. M... on contact with pressure

Tolerance and Habituation. Rep... peated use.

USES

(1) As an analgesic with air (in Cyprane or Duke Inhaler)
(2) For light anesthesia not deeper than first plane in combination with nitrous oxide by the semi-closed technique.

ADVANTAGES

(1) Is potent analgesic for obstetrics and minor surgery
(2) Is not flammable.
(3) Not unpleasant to inhale.
(4) Inexpensive.
(5) May be used for ambulatory patients

DISADVANTAGES

(1) Not satisfactory as surgical anesthetic for major surgery
(2) Cannot be used in the closed system.
(3) Muscle relaxation poor
(4) Is cardiotoxic and causes disturbances in cardiac rhythm.
(5) May be hepatotoxic.
(6) Vaporizes with difficulty

FLUOTHANE (HALOTHANE)

SYNONYMS—Halothane

HISTORY—Synthesized by Suckling (1951) Basic animal studies reported by J Raventos (1956) Studies in man by Michael Johnstone (1956) and Bryce Smith and O Brien (1956) (all in England)

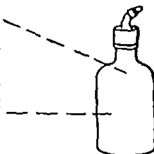
PROPERTIES

Physical—Clear, mobile liquid. S.G 1.86 (20°C.) B.P 50 2°C. at 760 mm. Hg Vapor pressure 241.5 mm. Hg at 20°C. Solubility 0.345 parts in 100 part H_2O at 20°C. Oil/water ratio 330.

Chemical—Stable Decomposes to various acid products if exposed to light. Stabilized by addition of thymol (0 01%) Presence of fluorine on carbon 1 stabilizes of chlorine and bromine on carbon 2.

Impurities—Decomposed by acids int halogenated acids.

Storage—In dark bottles.

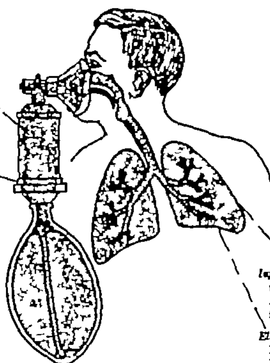


ADMINISTRATION

By semi-closed, non-rebreathing technique using precision calibrated heat compensated vaporizers. Inhaled concentration difficult to control in both closed system and open techniques. Not decomposed by soda or Baralyme.

Induction—Smooth without struggling Stage II quiet and uneventful. Induction and recovery rapid. Less than 4 minutes in short procedures. 0.5-2.5% required for induction. Maintenance accomplished with 0 4-1.5%.

Maintenance—Little additional agent necessary after induction Not easily controlled unless temperature compensated vaporizers are used. Conventional draw-over type of vaporizer not satisfactory particularly in closed system.



Inflammability—Vapors not flammable when mixed with air nitrous oxide or oxygen. Azeotropic mixture with ether (31%) fluothane (69%), not flammable.

Elimination—Not altered within the body Major portion eliminated through lungs. Recovery occurs within 5-6 minutes. Minute traces persist on exhalation due to elimination of drug absorbed by adipose tissues. Longer recovery period in long anesthesia (up to 20 minutes)

USES

When non-flammable anesthetic is desired

ADVANTAGES

(1) Non-flammable.
(2) Non-irritating.
(3) Non-spasmogenic to larynx and bronchi.
(4) Rapid induction and recovery
(5) Potent—more potent than chloroform.
(6) Chemically stable.
(7) Fortifies nitrous oxide.

DISADVANTAGES

(1) Overconcentration leads to circulatory collapse.
(2) Expensive.
(3) Difficult to use in closed systems or by open-drop method.
(4) Depresses respiration and circulation.
(5) Enhances ganglionic blockade.

FLUOTHANE

Brain—Depresses from above downward. Sensorium clear after recovery. Follows stages and planes according to Guedel. Electroencephalogram similar to ether—7 levels:

Level I—Fast frequency low voltage activity as consciousness is lost.

Level II—Slow frequency 2-4 cycles per second; high voltage of 50 microvolts in light surgical. Fast-low voltage activity superimposed.

Level III—Slow waves 4 cycles per second amplitude of 50–100 microvolts.

Level IV—Fast activity disappears 2-6 cycles per second, 50–100 microvolts.

Level V—Slow waves 1 cycle per second 100–200 microvolts interposed with smaller faster waves 15-30 minutes, 2-6 cycles per second.

Level VI—Slow wave frequency 2-6 cycles per second, amplitude 15 microvolts. First burst suppression.

Level VII—Absence of any wave forms.

Vomiting Center—Depressed during anesthesia. Nausea and emesis uncommon in post-anesthetic period.

Cough Center—Obtunded.

Respiratory Center—Depressed by deep anesthesia. Respiratory arrest precedes cardiac arrest. Response to 5% CO_2 diminishes with increasing depth.

Vasomotor Center—Some depression giving rise to hypotension.

Vagus Center—Vagal action preserved or enhanced. Bradycardia develops. Atropine premedication desirable.

Carotid Body—Remains active.

Lungs—Respirations deep and regular in upper stages. Depressed in lower stages. Tidal volume decreases as anesthesia deepens. Rate increased to compensate for decrease; therefore, minute volume unchanged. End expired CO_2 tensions rise as anesthesia deepens. Premedicants enhance respiratory depression.

Bronchi—Not spasmogenic. No irritation, cough or secretions.

Metabolism—Decreased. Body temperature falls due to decreased activity.

Liver—Moderate increase in bromsulphthalein retention (same as ether less than chloroform). Thymol turbidity unchanged after 5 days. No hepatic necrosis or hemolysis. Serum transaminase unchanged after 12-80 hours.

Adrenal—Sympathetic activity not depressed.

Kidney—Urea clearance not affected. Blood urea remains normal. No microscopic changes in urine.

Blood—Volume unchanged. Bleeding and clotting time changed. Decreased oozing due to hypotension.

Cells—No changes in morphology.

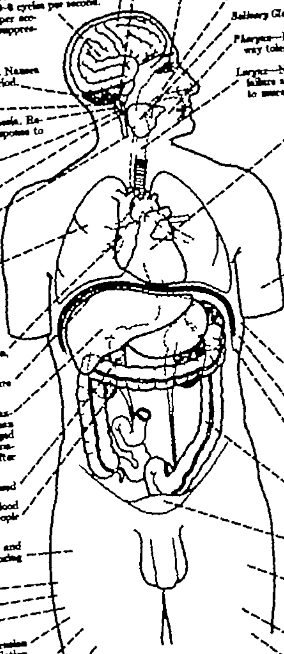
Sugar—Moderate elevation.

Urea—No change.

Gases—Total CO_2 content and CO_2 tension rises as anesthesia deepens and ventilation is decreased.

Concentration—Blood E.E.G. level I—8.8 mgm. per 100 cc. Level II—8.5 Level III—7.1; Level IV—9.2 Level V—20.1

Pathology—No specific lesions ascribable to drug.



Intracranial Pressure—Not elevated to any significant degree. Satisfactory for neurological surgery.

Temperature Regulating Center—Depressed in surgical stages of anesthesia.

Eye—Lid reflex disappears Stage IV plane 1. Pupils contract in Stage III. Do not dilate as anesthesia deepens. Rotation of eyeballs ceases at plane 2. Corneal reflex remains active plane 1 and 2. Pupils dilate in deep anesthesia.

Mucous Membranes—Not irritated by inhaled anesthetic concentration.

Salivary Glands—Not stimulated. Absence of secretions.

Pharynx—Reflex disappears in plane 1. Pharyngeal airway tolerated.

Larynx—Not spasmogenic. Spasm uncommon after failure at intubation. Tube tolerated. Non-irritating to mucous membranes in anesthetic concentrations.

Heart—Depresses myocardium. Causes decrease in cardiac output. Slows bradycardia—10% decrease in pulse rate. Varies directly with concentration. Arrhythmias appear in deep anesthesia with all techniques. Escape may occur. Ventricular extrasystoles may appear. Ventricular tachycardia may develop. Nodal rhythm and escape may occur. Heart sensitized to pressor amines, particularly epinephrine and norepinephrine.

Blood Pressure—Hypotension consistently observed. Proportional to concentration. Greater during induction than during maintenance. Probably result of decreased cardiac output and depression of vasomotor center. Ganglionic blockade may also play minor role. Not reversed by atropine.

Hypotension disappears during maintenance, unless overconcentration produces myocardial depression.

Autonomic Nervous System—Not a po[…] ganglionic blocking agent by itself, bu[…] tentiates ganglionic blockade by [...] methonium and d-tubocurarine.

Venous Pressure—Tends to increase.

Arterioles—Some increase in periphera[…] sistance indicating some sympatheti[…] tivity.

Gastro-intestinal—Nausea and vomiting [...] common. Depresses visceral smooth [...]cle.

Uterus—Inhibited progressively as [...]thesia deepens. Recovers as it lig[...]. Drug passes placental barrier.

Muscle—Concentrations up to 4.0% [...] paralyze myoneural junction. Antag[...] succinyl choline effect slightly an[...] tentiates d-tubocurarine. Relaxatio[...] quate for major surgery.

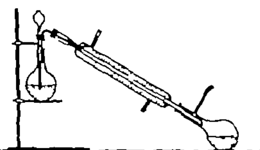
Body Temperature—Decreased due to [...]sion of heat regulating center.

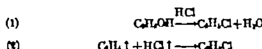
Skin—Temperature elevated. Vasodil[...] Dry, warm, pink. No blistering w[...]plied locally.

ETHYL CHLORIDE

HISTORY—Prepared by Basil Valentine in 17th century Anesthetic properties discovered by Pierre Flourens of France in 1847 P Redard of Switzerland in 1888 introduced it as a spray for local anesthesia. H J Carlson Swedish dentist accidentally caused general anesthesia in man while using a spray for local anesthesia Used for general anesthesia by Redard in 1888 in Switzerland.

PREPARATION—(1) By reacting ethylene with gaseous hydrogen chloride. (2) By refluxing ethyl alcohol with hydrochloric acid and zinc chloride





$$(1)\quad C_2H_5OH \xrightarrow{HCl} C_2H_5Cl + H_2O$$

$$(2)\quad C_2H_4\uparrow + HCl\uparrow \longrightarrow C_2H_5Cl$$

PROPERTIES

Physical—Gas at ordinary temperature which easily compresses to a clear limpid fluid, possessing an ethereal odor Non-irritating. Boiling point 12.5–13°C.; molecular weight 64 specific gravity 0.921 at 0°C Specific gravity of vapor 2.28 (air equals 1); vaporization reduces temperature to below freezing. Temperature attained is between −15–20°C. Soluble in alcohol and ether 1 cc. of liquid in 4 liters air = 7% mixture of vapor

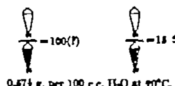
Chemical—Hydrolyzed by acids and alkalis to alcohol. Decomposed by light and heat in the presence of water Burns with green flame.

Stability—Stable at room temperature. Decomposed by light and air

Impurities—Aldehydes, hydrochloric and acetic acids, and ethyl alcohol.

Storage—Store in amber container as liquid under slight pressure Equipped with a fine capillary nozzle and tight cap allowing a fine spray two or three feet long to ensue Keep in cool place Included in U.S.P XIII Also known as *Kelene*, *narcotyl chlorid*, mono chlor ethane

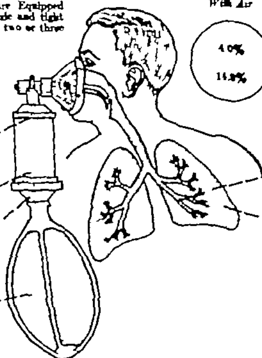
Solubility—Possesses high lipoid solubility: at 38°C., 2 volumes of vapor dissolve in 1 volume of blood. Slightly soluble in water



0.574 g. per 100 c.c. H_2O at 20°C.

Inflammability—Ignition temperature 517°F 1 pound with air makes 147 cubic feet of explosive vapor at 60°F at normal pressure. Minimum ignition temperature in air 966°F.; in oxygen 874°F

With Air	*With Oxygen*	*In Nitrous Oxide*
4.0%	4.05%	2.10%
14.8%	67.2%	32.8%



Stability in Absorber—Hydrolyzed slowly by the alkali into chlorides and ethyl alcohol

ADMINISTRATION

Open-drop, or closed technique Ice from condensed water vapor forms on mask when used by open-drop method.

Induction—Rapid, 1 to 2 minutes Pleasant and easy to inhale No excitement.

Effective Concentrations of Inhaled Mixtures—Analgesia—2 to 3% anesthesia—3.0% to 4.5% respiratory failure 6%.

Elimination—Major portion eliminated unchanged in urine, feces, sweat and exhalations. Recovery from anesthesia rapid requiring 1 to 2 minutes. Minute traces remain in blood for some time after discontinuing anesthesia. Greatest portion exhaled. Possibility of decomposition of some portion in body not disproved.

Diffusion—Absorbed from isolated lung lobule in 15 minutes (air = 16 hrs.)

Cortex—Pathways from periphery blocked. Reflexes and motor activity abolished in stage III

Respiratory Center—Depressed. Respiration fails before circulation.

Vasomotor Center—Depressed in deep anesthesia or in overdosage Ordinarily not affected.

Cough Center—Depressed during third stage anesthesia.

Vagus Center—Stimulated at first depressed in deep anesthesia.

Vomiting Center—Depressed. Post-anesthetic vomiting infrequent.

Lungs—Alveolar membrane locally stimulated. Hyperpnea occurs in first plane followed by respiratory depression. Pulmonary and bronchial epithelium not irritated to any marked extent.

Liver—May reduce liver function. May cause hepatitis.

Sphincters—Relaxed only in deep anesthesia.

Skeletal Muscles—Relaxation of large muscles obtained with difficulty Spasticity may occur Opisthotonos and rigidity not infrequent during induction.

Skin—Pallor in deep anesthesia due t vasomotor collapse Ashen grey cyanosis not uncommon in collapse

Blood—Concentration, 20 mgm. per 100 cc for light anesthesia 30 mgm for deep anesthesia 40 mgm lethal. Margin of safety narrow

Intracranial Pressure—Increased slightly Not of significance without anoxia.

Eyes—Eyeballs continue to rotate int 3rd plane Pupils dilated in stage II; constricted in stage III. Eye signs not a reliable guide t depth.

Mucous Membranes—Slightly irritated. Ciliary activity depressed. Secretions absent.

Pharynx—Pharyngeal reflex depressed in first plane Airway tolerated. Spasm of pharyngeal muscles common.

Salivary Glands—Slight increase in secretion during induction abolished during anesthesia.

Larynx—Cough reflex abolished in deep anesthesia reflex spasm of glottis frequent if infection or mucus is present in upper respiratory tract. Laryngeal reflex abolished in 2nd plane.

Heart—Primary decrease in rate (vagal effect) followed by increase Cardiac output decreased an average of 18% Myocardium depressed directly Ventricular fibrillation may occur early due to increased irritability of automatic tissue; arrhythmias enhanced by epinephrine Ventricular fibrillation may occur during induction. Overdosage results in asystole from myocardial depression.

Blood Pressure—Decreased in deep anesthe sia due t peripheral dilatation from de pressed vasomotor center

Gastro-Intestinal System—Decreased acti of these organs.

General pharmacological effects of ethyl chloride are similar but less intense than those of chloroform. Circulatory failure may occur before respiratory failure

USES

(1) For analgesia for minor operations (exodontia, obstetrics)
(2) For anesthesia for short surgical procedures.
(3) As a preliminary to open ether anesthesia to shorten second stage
(4) As a complement to nitrous oxide or ethylene anesthesia.
(5) As a spray to cause local anesthesia by the production of cold.

CONTRAINDICATIONS

(1) Presence of cautery or other sources of ignition.
(2) Presence of cardiac, renal or hepatic disease
(3) Presence of upper respiratory infections.
(4) Procedures expected to last more than several minutes.

ADVANTAGES

(1) Period of induction and recovery rapid.
(2) Shortens length of stage II of ether anesthesia during induction.
(3) Requires simple or minimum of apparatus.
(4) Allows use of air as diluent and source of oxygen.
(5) Does not cause respiratory depression.
(6) Chemically stable and inexpensive
(7) Severe or prolonged post-anesthetic vomiting absent.

DISADVANTAGES

(1) Possesses a narrow margin of safety
(2) Causes circulatory depression, particularly affecting the heart.
(3) Forms explosive mixtures with air or oxygen.
(4) Frequently causes muscle rigidity and stridor
(5) Depth of anesthesia not easily maintained at a constant level.
(6) May cause renal or hepatic damage

MIXTURES OF HALOGENATED HYDROCARBONS

ANESTHOL—Ethyl chloride 17%, chloroform 36%, diethyl ether 47%.

SCHLEICH'S MIXTURE—Same three drugs in different proportions.

SOMNOFORM—Ethyl chloride 35%, methyl chloride 60%, methyl bromide 5%.

NOVANEST—Ethyl chloride, methyl chloride, chloromethylene, diethyl ether

ANESTILE—Ethyl chloride and methyl chloride

A.C.E. MIXTURE (Alkaform)—Alcohol 16%, chloroform 34%, ether 50%.

LESSER KNOWN HALOGENATED HYDROCARBONS

Drug	Chemistry	Properties	Uses	Comment
Methyl chloride (monochlormethane)	Clear colorless, odorless gas. B.P −24°C. Compresses to a colorless liquid. Burns with a green flame	Slightly narcotic and anesthetic when inhaled. Rapid acting, and rapid recovery	As a refrigerant.	Toxic for clinical use. Decomposes to methyl alcohol in body. Toxic to lungs and nerve tissue. Toxic manifestations appear hours or days after inhalation.
Methyl dichloride (dichlormethane)	Clear colorless liquid. B.P 40–41	More narcotic than methyl chloride. Not inflammable. Soluble—1 50 water at 25°	As a spray for local anesthesia. As a refrigerant.	Toxic to liver lung and nerve tissue. Same objectional features as methyl chloride. Neurodegeneration may persist and cause permanent damage. Does not form methyl alcohol.
Carbon tetrachloride (tetrachlormethane)	First prepared by Regnault in 1839. Clear colorless non-inflammable liquid. B P 76°C.	Potent narcotic if inhaled.	Anthelmintic agent — Fire extinguisher	Possesses narrow margin of safety. Hepatotoxic. Vaporized slowly. Does not form methanol in body. Not suitable for surgical anesthesia.
Methyl bromide (monobromomethane)	Clear colorless, odorless gas. B.P 4.5°C.	Mildly narcotic, irritant.	As refrigerant and insecticide	Short or prolonged periods of inhalation cause pulmonary irritation and various neurological changes. Toxic manifestations delayed for hours or days. Decomposes to methanol in body
Bromoform (tribromomethane)	Prepared by Löwig in 1832. Colorless, heavy liquid. B P 150°C.	Potent narcotic. Like chloroform in action but with narrower safety margin.	Not used clinically. Formerly used as an antispasmodic for cough.	Hepatotoxic. Not stable—decomposes to free bromine and other brominated compounds. Vaporizes slowly with difficulty. Not inflammable.
Ethyl bromide (monobromoethane)	Colorless liquid with ethereal odor B.P 38. Inflammable. Not stable in presence of heat, light and air	Narcotic, similar to ethyl chloride. More potent. More toxic.	As surface anesthetic. Inhalation anesthetic similar to ethyl chloride.	Possesses narrow margin of safety. Rapid induction and recovery. May cause pulmonary irritation.
Ethylene dichloride (dichlorethane)	Colorless, oily liquid with pleasant odor and sweet taste. Boils 83–85°C.	Possesses narcotic properties.	Not used clinically	Potency approaches that of chloroform. More potent than ethyl chloride
Ethylene dibromide (dibromethane)	Colorless, heavy liquid. B P 131 C chloroform-like odor. Unstable in presence of light, heat and air	Narcotic.	As solvent. Not clinically important.	Causes degenerative changes in viscera. Irritates skin and mucous membranes.
Vinyl chloride (monochlorethylene)	Colorless gas with ethereal odor. B.P 13–14°C inflammable	Narcotic and anesthetic similar to ethyl chloride.	As a solvent.	Possibility as surgical anesthetic not completely investigated. May be hepatotoxic. Causes pulmonary irritation in animals.
Dichlorethylene	Colorless liquid with slightly ethereal odor B.P 55°	Narcotic and anesthetic.	Not clinically important.	Irritating, causes nausea, cramps, irritating to skin.
Tetrachlorethylene	Clear colorless liquid. B P 121° Non-inflammable	Possesses anesthetic properties	Tried clinically by Angus. Found unsuitable	Slow induction causes profuse secretions. Difficult to vaporize. Not stable. Irritates skin. Difficult to maintain even plane of anesthesia.
Anesthol	Clear colorless liquid.	Produces general anesthesia.	For inhalation anesthesia.	Ethyl chloride 17 parts, chloroform 36, ethyl ether 47
Somnoform	Clear colorless liquid.	Produces general anesthesia	For inhalation anesthesia.	Methyl chloride 60 parts, ethyl bromide 5, ethyl chloride 35.
Alcoform (A.C.E. mixture)	Clear colorless liquid.	Produces general anesthesia	For inhalation anesthesia.	Chloroform 34, alcohol 16, ether 50.

SECTION VII. INORGANIC NONVOLATILE AGENTS

BROMIDE ION

Cortex—Depresses. Induces sleep which is never deep. Mental processes dulled. Motor cortex depressed. "Psychotic" symptoms in chronic intoxication. Electroencephalogram shows depression of waves.

Lungs—Respiration slowed as in normal sleep.

Kidney—Eliminates bromide ion and chloride ion in same ratio as it exists in plasma. Bromidism causes depletion of chloride ion.

Genitalia—Sex instinct depressed by large doses.

Tissues—Bromide ion indifferent to most tissues except brain. Body does not differentiate between chloride and bromide ions.

Thalamus—Not analgesic. Large doses may cause anesthesia.

Eye—Loss of conjunctival sensitivity and wink reflex.

Pharynx—"Gag" reflex reduced by large doses.

Heart—No significant action.

Blood Pressure—Not affected. May reduce if elevated from psychic causes.

Gastrointestinal Tract—Irritated mucosa may cause nausea. Readily absorbed and distributed like Cl ion.

Reflexes—Reduced. Peripheral sensory organs unimpaired.

Skin—Rashes frequent.

DOSE—1-4 grams. Single doses of no value. Cumulative action results in "bromism" if administered over prolonged period.

PREPARATION—Used as salt of potassium, sodium, calcium or ammonia. A mixture known as triple bromide may be used. Potassium bromide is included in the U.S.P.

MAGNESIUM ION

The magnesium ion occurs in aqueous solutions of soluble salts of magnesium. Magnesium is a normal constituent of blood and other tissues. High concentrations in blood depress the central nervous system.

Cortex—Depresses if administered parenterally. Mild at 10 mgm.% in serum. Anesthesia at 20 mgm.% Reversed by calcium intravenously.

Cord—Induces spinal analgesia if administered intrathecally. Depressed when large amounts are administered intravenously.

Heart—Depressant to heart muscle. High concentrations cause bradycardia, arrhythmias and cardiac arrest. Action antagonized by calcium.

Respiration—Paralyzed by large parenteral doses. Fails before circulation.

Blood Pressure—Falls after toxic doses.

Gallbladder—Hypertonic solutions injected into duodenum increase flow of bile.

Gastrointestinal Tract—Absorbed with difficulty. Oral doses do not raise serum level. Absorption enhanced by acid reaction in intestine; retarded by alkaline. Causes withdrawal of water and catharsis.

Kidney—Ion easily and rapidly eliminated after oral ingestion. In presence of renal disease excretion impaired. Toxic amounts may cause depression simulating uremia.

Muscle—Possesses a curare-like action. Excitation of striated muscle by nerve impulses prevented. Present in high concentration—21 mgm.% in muscle cells.

Blood—Normally present in 2–3 mgm.%; 80% ionized and diffusible; remainder bound to protein. Concentration in red cells higher than serum.

Nerve—High concentrations locally applied block conduction. Concentrations necessary too high for safety.

Skin—Used as compress in hypertonic solution in infection to dehydrate area.

PREPARATION—Used as the sulphate 10 cc. of a 25% solution intramuscularly for adults or 2 cc. of a 25% per 20 lbs. body weight. Two per cent solutions are isotonic.

USES

Control convulsions caused by encephalopathies. Action augmented by morphine, ether and other central nervous system depressants. Used with rectal ether and morphine.

ADMINISTRATION

Usually administered intramuscularly. Local anesthetic effect minimizes pain of injection.

SECTION VIII. ALIPHATIC NONVOLATILE AGENTS

ETHYL ALCOHOL

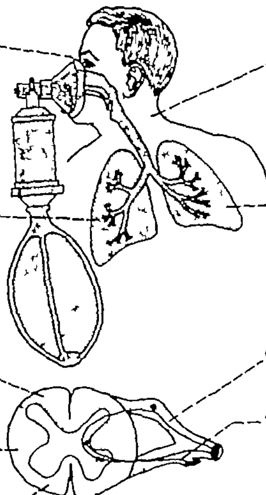
PROPERTIES—Ethyl alcohol is a colorless, mobile, inflammable fluid possessing a burning taste and pleasant odor. Absorbs water from air. S.G. 0.798 at 15°C. B.P. 78.5°C. Solidifies below −130°C. Flash point between 9 and 11°C. Formula C_2H_5OH. M.W. 46.05. Made by fermentation of starches and synthetically from acetylene or ethylene. Also known as ethanol or hydroxy ethane.



PREPARATION—Anhydrous, absolute or 100% for nerve blocking. Alcohol U.S.P. 92.5% by weight or 94.9% by volume. Alcohol, diluted U.S.P. 49.9% by volume. Alcohol and dextrose—5% alcohol and 5% dextrose in distilled water for intravenous administration.

Brain and Cord—Irregular descending depression. Never a stimulant. General anesthesia results after unconsciousness is established. Brain absorbs drug. Brain level reaches peak after blood level.

Distribution in Tissues—Passes into all tissues and body fluids. Concentration in brain and spinal fluid rises and falls at a slower rate than in other tissues.



Tolerance—Tolerance develops after repeated use. Cross tolerance to allied aliphatic anesthetics and hypnotics such as ether, avertin, cyclopropane, etc. occurs. Addiction may occur after prolonged continued use, particularly in individuals having psychopathic personality.

Fate—Small amounts completely oxidized. Large amounts cause appearance of intermediate products (aldehyde, acetic acid) which appear in breath and urine. Approximately 10 cc. oxidized per hour. Oxidation accelerated by glucose and insulin. Alveolar air concentration of 1 mgm. per liter indicates intoxication.

Sensory Nerves—Temporarily destroyed by 90% concentration. Nerve fibres regenerate in due time. Varies upon size and degree of destruction and the nerve.

Cell Body and Ganglia—Attacked and destroyed.

Motor Nerves—Require more concentrated solution for destruction than sensory or autonomic nerve fibres.

Perineural Injections—Five cc. absolute alcohol into soft tissue causes an area of necrosis 1 cm. in diameter. Histologic degenerations of nerve similar to that obtained when nerve is sectioned. Similar to Wallerian degeneration. Neuritis and sclerosis follows.

Autonomic Nerve Fibres—Destroyed with same efficacy as sensory nerves.

Bactericidal Action—60 to 90% kills non-sporulating bacteria. 70% most effective; 95% not as effective as more dilute solutions.

Cortex—Depressed. Ability to concentrate and discriminate are diminished. Memory and insight dulled. Behavior depends upon the personality of individual, tolerance to drug and presence of extraneous stimuli.

Temperature Regulating Center—Depressed especially with large doses.

Medulla—Depressed. Anesthetic dose and dose necessary to cause respiratory failure close to each other. Possesses a narrow margin of safety.

Vasomotor Center—May be depressed, causing vasodilatation.

Respiratory Center—Narcotic doses depress. Small doses have no effect. Intoxicating doses paralyze center.

Lung—No remarkable effects. May be absorbed from pulmonary alveoli if vaporized. 0.5 to 2% may be eliminated here. Not a chief avenue of elimination. Respiration is stimulated by small doses reflexly. Ordinary doses do not affect ventilation. Minute volume exchange decreased during marked intoxication.

Bronchioles—Unaffected.

Metabolism—Decreased only when large amounts are injected and sleep follows. Acts as substitute for carbohydrates.

Liver—Depresses liver function. Dye excretion impaired causes depletion of glycogen. Inhibits reconversion of lactic acid to glucose. Prolonged continued use may cause parenchymal damage if pre-existing liver disease is present. Drug oxidized here.

Bile—Minute amounts excreted into bile.

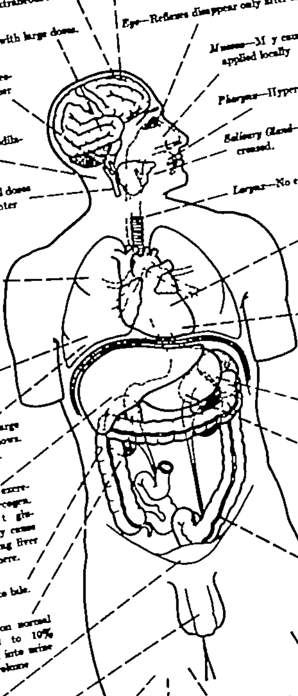
Kidney—No pathological effect on normal kidneys. Induces diuresis. 2 to 10% may be eliminated unchanged into urine. Amount in urine varies with volume.

Uterus—No significant effects.

Genitalia—Possesses no aphrodisiac power. May decrease sexual power.

Nerves—General depression of reflex activity follows intoxicating doses. Reflex activity depressed.

Body Temperature—Falls due to increased heat loss from dilatation of cutaneous veins and depression of temperature regulating center.



Intracranial Pressure—Not altered unless blood pressure falls. Prolonged increase of secretion of spinal fluid may be cause of cerebral edema in chronic alcoholism.

Eye—Reflexes disappear only after massive doses.

Mucosa—May cause irritation and inflammation when applied locally.

Pharynx—Hyperemia results if applied locally.

Salivary Gland—Usually stimulated. Flow of saliva increased.

Larynx—No effect.

Heart—No direct cardiac stimulation. Small doses increase pulse rate. No direct effect on myocardium ordinarily. Toxic doses depress. Dilatation of coronary vessels.

Blood Pressure—Systolic pressure rises and diastolic falls with small doses. Large doses lower systolic and elevate diastolic. Toxic doses depress vasomotor center causing hypotension.

Venous Pressure—No effect. Thrombosis of veins in intravenous use.

Stomach—Oral ingestion causes hyperemia of gastric and intestinal mucosa. Reflexly stimulates secretion by reflex action. 10% solution causes secretion of juices rich in acid but poor in pepsin. No effect on motility. Above 20% secretion may be depressed. Alcohol used as solvent for drugs (elixirs) may stimulate absorption of all substances from gastrointestinal tract.

Intestines—Approximately 80% absorbed here. Rate of absorption varies with concentration. Rapidly absorbed from small bowel. No effect on intestinal digestion. May be absorbed through colonic mucosa.

Muscle—No increase in muscular activity. Relaxed in overintoxication.

Skin—No absorption through skin. Locally applied causes cooling by evaporating. Rubbing causes counter irritation and rubefacient action. Hardens on repeated application. Cutaneous vessels dilated by large oral doses causing flushing.

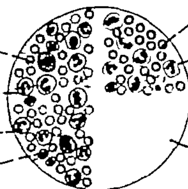
BLOOD

Oxygen Content—Unchanged in arterial blood unless severe depression of respiration occurs.

Oxygen Capacity—Unchanged.

Lactic Acid—Increased.

Glucose—Unchanged. May increase in severe intoxication.



Carbon Dioxide Content—Unchanged. May be slightly elevated.

Carbon Dioxide Combining Power—Unchanged. May be decreased slightly in mild intoxication and increased in deep.

Blood Concentration—Peak reached after first hour in single administration. Plasma contains twice as much as corpuscles. 200 mgm.% usually indicates mild or moderate intoxication, 300 mgm. intoxication, 400 mgm. advanced intoxication. 500–800 mgm. is fatal concentration. Concentration required to cause intoxication varies from one individual to next. Traces remain in blood for as long as 24 hours. Work does not influence blood levels.

USES

(1) As a solvent for drugs for oral use (elixirs)
(2) As a bactericide locally applied.
(3) For interrupting nerve fibres (by local or intraspinal injection)
(4) As hypnotic and sedative by oral or intravenous route
(5) To secure vasodilatation in peripheral vascular disease.

CONTRAINDICATIONS AS A HYPNOTIC OR ANESTHETIC

(1) Hepatic and renal disease
(2) Urinary tract infection
(3) Ulcerations of gastrointestinal tract.

ADVANTAGES

None as an anesthetic.

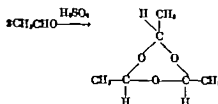
DISADVANTAGES AS A HYPNOTIC OR ANESTHETIC

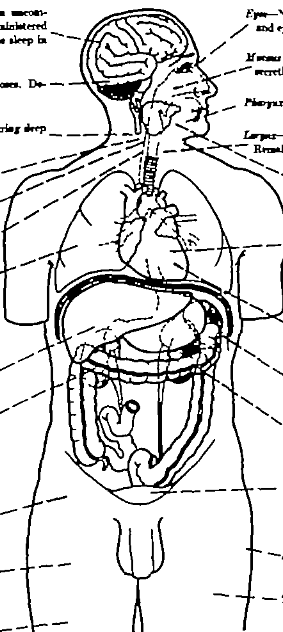
(1) Anesthetic concentration is close to the lethal concentration.
(2) Response varies from subject to subject.
(3) Onset of narcosis variable and often delayed.
(4) Duration of action variable.
(5) Non-controllable
(6) Causes slough and neuritis when injected locally
(7) Causes thrombosis of veins when used intravenously

PARALDEHYDE

HISTORY—Introduced by Cervello in 1882. Intravenous use reported by H. Noel and H. S. Soutar in 1913.

PREPARATION—By interaction of acetaldehyde and concentrated sulphuric acid. Three molecules of the aldehyde polymerize to form one molecule of paraldehyde. Empiric formula is $(CH_3CHO)_3$. Structural formula is





Cortex—Depressed. Excitement and delirium uncommon. Not analgesic. Restlessness when administered in presence of pain. Large doses may cause sleep in presence of pain. Few or no after effects.

Vasomotor Center—No effect in sedative doses. Depressed during deep hypnosis.

Cough Center—Remains active. Depressed during deep hypnosis.

Respiratory Center—Depressed by large doses. Respiratory failure precedes circulatory failure.

Vomiting Center—Not stimulated.

Carotid Sinus—Sino aortic mechanism remains active.

Lungs—Respiratory rate increased in light hypnosis, decreased in deep. Amplitude decreased. Minute volume exchange decreased. Hering-Breuer reflex intact. Epithelial lining irritated. Drug (11–[illegible]%) exhaled from the lung unchanged.

Liver—Untoward results not reported. Up to 80% oxidized here.

Kidney—Oliguria in deep hypnosis. Diuresis may follow in recovery period. Drug excreted in urine; concentration parallels plasma level.

Skeletal Muscles—No effect in hypnotic doses. Relaxed in deep hypnosis. Relaxation not satisfactory for major surgery.

Reflexes—Superficial and deep remain active during sedation. Obtunded by deep hypnosis. Knee and ankle jerk remain active in deep hypnosis.

Body Temperature—No notable effect. Decreased 1 to 2°F in deep hypnosis.

Eyes—No notable effect during sedation. Pupils dilated and eyeball movements abolished in deep hypnosis.

Mucous Membranes—Irritated locally causing copious secretion of mucus.

Pharynx—"Gag" reflex abolished in deep hypnosis.

Larynx—Cough reflex abolished during deep hypnosis. Remains active during light hypnosis and sedation.

Salivary Glands—Stimulated at first due to local irritation. Depressed during deep hypnosis.

Heart—No significant effect during sedation or hypnosis. Rate slightly increased. Rhythm not altered. Circulation time prolonged in deep hypnosis. Massive doses depress the myocardium.

Blood Pressure—No significant changes during sedation or mild hypnosis. Falls during deep hypnosis or overdosage.

Spleen—Contracted during deep hypnosis. No significant effect during sedation.

Gastrointestinal Tract—Inhibition of movements in deep hypnosis.

Uterus—Contraction of the intact organ not increased by hypnotic doses. May be decreased during deep hypnosis. Drug passes through placenta to fetus causing depression of fetal respiration.

Skin—Temperature decreased. Slight trace in perspiration.

Tissues—Drug distributed uniformly in all tissues, muscle, heart, kidney, liver and brain. Cumulative action may follow repeated use.

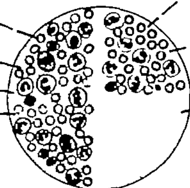
BLOOD

Red Cells—Hemoconcentration during deep hypnosis. Causes hemolysis when administered intravenously.

Sedimentation Rate—Unchanged.

Bleeding Time—Unchanged.

Clotting Time—Unchanged.



Oxygen Capacity—Increased during deep hypnosis. Content reduced during deep hypnosis from respiratory depression.

Blood Sugar—Unchanged during sedation. Increased during deep hypnosis.

Carbon Dioxide Combining Power—Reduced during deep hypnosis.

PROPERTIES

Clear colorless, mobile liquid, possessing a pungent odor. Odor clings to surrounding objects for days. Specific gravity 0.995 at 20°C. Boiling point 124°C. *Burns when ignited. Solubility* 1 to 8 in water at 20°C. Highly soluble in fats and alcohol. Acids decompose it to acetaldehyde. Self sterilizing and remains sterile. Does not possess chemical reactions of aldehydes. Included in the U.S.P. XIII.



Impurities—Acetaldehyde, ethyl alcohol, acetic and other organic acids. Stable under ordinary circumstances.

Storage—In dark bottles. Protected away from light, heat and air.

ADMINISTRATION

Orally—For hypnosis, 5 cc. with flavoring. *Rectally*—For hypnosis, 15 to 30 cc. in equal volume of saline (often used with 1 cc. benzyl alcohol to alleviate local irritating effects). *Intravenously*—For rapid sedation 5 to 10 cc. (deep hypnosis lasts several minutes, followed by sleep lasting an hour or more). Not recommended for surgical anesthesia.

Tolerance—Habituation uncommon. Cross tolerance develops between it and alcohol and aliphatic hypnotics. Addiction uncommon.

USES

(1) As a hypnotic particularly in chronic alcohol addicts and mentally disturbed patients.
(2) As a basal narcotic preliminary to surgery.
(3) As a rectal analgesic and amnesic for obstetrics.
(4) As an anti-convulsant.
(5) As a solvent for other drugs—barbiturates.

CONTRAINDICATIONS

(1) Broncho pulmonary disease—excreted by lungs.
(2) Hepatic and renal insufficiency.
(3) Gastro-intestinal diseases. Irritates mucosa.

ADVANTAGES

None. Erroneously considered a safe hypnotic with wide margin of safety.

(1) Sleep sets in promptly (10–15 minutes). Resembles normal sleep. Lasts 5 to 6 hours.
(2) No after effects.
(3) Delirium uncommon.
(4) Prompt onset of action.

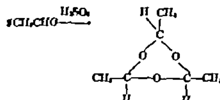
DISADVANTAGES

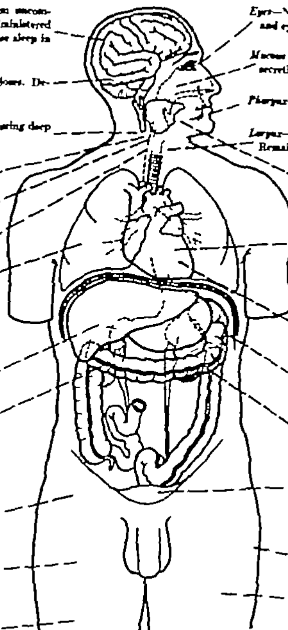
(1) Possesses an unpleasant odor and is disagreeable.
(2) Variability of action.
(3) Lack of analgesic power.
(4) Narrow margin of safety in large doses.
(5) Irritates mucosa of mouth, stomach or rectum.
(6) Basal hypnosis disturbs metabolism. Possibility of tolerance and addiction.

PARALDEHYDE

HISTORY—Introduced by Cervello in 1882. Intravenous use reported by H. Noel and H. S. Souttar in 1913.

PREPARATION—By interaction of acetaldehyde and concentrated sulphuric acid. Three molecules of the aldehyde polymerize to form one molecule of paraldehyde. Empiric formula is $(CH_3CHO)_3$. Structural formula is





BLOOD

Red Cells—Hemoconcentration during deep hypnosis. Causes hemolysis when administered intravenously.

Sedimentation Rate—Unchanged.

Bleeding Time—Unchanged.

Clotting Time—Unchanged.

Oxygen Capacity—Increased during deep hypnosis. Content reduced during deep hypnosis from respiratory depression.

Blood Sugar—Unchanged during sedation. Increased during deep hypnosis.

Carbon Dioxide Combining Power—Reduced during deep hypnosis.

PROPERTIES

Clear colorless, mobile liquid, possessing a pungent odor. Odor clings to surrounding objects for days. Specific gravity 0.989 at 20°C. Boiling point 124°C. Burns when ignited. Solubility 1 to 8 in water at 20°C. Highly soluble in fats and alcohol. Acids decompose it to acetaldehyde. Self sterilizing and remains sterile. Does not possess chemical reactions of aldehydes. Included in the U.S.P. XIII.

Impurities—Acetaldehyde, ethyl alcohol, acetic and other organic acids. Stable under ordinary circumstances.

Storage—In dark bottles. Protected away from light, heat and air.

ADMINISTRATION

Orally—For hypnosis, 5 cc. with flavoring. *Rectally*—For hypnosis, 15 to 30 cc. in equal volume of saline (often used with 1 cc. benzyl alcohol to alleviate local irritating effects). *Intravenously*—For rapid sedation 5 to 10 cc. (deep hypnosis lasts several minutes, followed by sleep lasting an hour or more). Not recommended for surgical anesthesia.

Tolerance—Habituation uncommon. Cross tolerance develops between it and alcohol and aliphatic hypnotics. Addiction uncommon.

USES

(1) As a hypnotic particularly in chronic alcohol addicts and mentally disturbed patients.
(2) As basal narcotic preliminary to surgery.
(3) As rectal analgesic and amnesic for obstetrics.
(4) As an anti-convulsant.
(5) As solvent for other drugs—barbiturates.

CONTRAINDICATIONS

(1) Broncho pulmonary disease—excreted by lungs.
(2) Hepatic and renal insufficiency.
(3) Gastro-intestinal diseases: irritates mucosa.

ADVANTAGES

None. Erroneously considered a safe hypnotic with wide margin of safety.

(1) Sleep sets in promptly (10–15 minutes). Resembles normal sleep. Lasts 5 to 6 hours.
(2) No after effects.
(3) Delirium uncommon.
(4) Prompt onset of action.

DISADVANTAGES

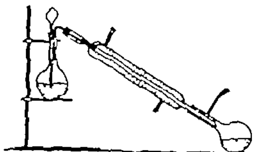
(1) Possesses an unpleasant odor and is disagreeable.
(2) Variability of action.
(3) Lack of analgesic power.
(4) Narrow margin of safety in large doses.
(5) Irritates mucosa of mouth, stomach or rectum.
(6) Basal hypnosis disturbs metabolism. Possibility of tolerance and addiction.

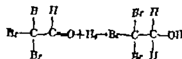
TRIBROMETHANOL (AVERTIN)

HISTORY—Produced by Willstätter and Duisberg in Germany in 1923. First used as an anesthetic by F. Eicholtz in man and animals in 1926. Clinical use promoted by Butzengeiger in 1927. Studied pharmacologically by Straub in 1928. Intravenous use reported by Martin Kirschner in 1929.

SYNONYMS—Bromethol, Rectanol, Ethobrom, E 107.

PREPARATION—Tribromacetaldehyde (Bromal) is first formed by treating ethyl alcohol with bromine. The bromal is then reduced with aluminum ethoxide in an atmosphere of nitrogen.





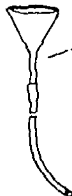
PROPERTIES

Physical—White crystalline powder possessing ethereal odor. Melting point 80°C. sublimes with decomposition. Poorly soluble in water. Soluble in organic solvents. Very soluble in amylene hydrate. 3.7 grams dissolve per 100 cc. H_2O at 37°C.

Chemical—Not stable. Decomposes easily, yielding dibromacetaldehyde and hydrobromic acid. Decomposition facilitated by heat, light, air and alkali. Decomposition detected by addition of indicator (Congo Red) which turns purple due to presence of acid.



Avertin Fluid—Tribromethanol plus amylene hydrate yields "avertin fluid." Included in U.S.P. XIII.



METHOD

Three per cent avertin fluid in pure water at 37°C. by enema, one-half hour pre-operatively. Average dose 60 to 80 mgm. per kilogram. Maximum total volume 6 to 8 cc. for females, 8 to 10 cc. for males. Children tolerate and require larger doses, approximately 100 mgm. per kilo. Doses causing complete anesthesia (150 to 600 mgm. kilo) cause marked depression, often fatal. Administer with patient on left side. Requires supplemental inhalation or regional anesthesia because reflexes are not completely abolished. *Surgical anesthesia* is not obtained except with dangerous dosages.

Elimination—Conjugated in liver with glycuronic acid. Product excreted in urine. 70 to 80% detoxified and eliminated in two to four hours. None eliminated via lungs or intestines. Conjugated product does not possess hypnotic properties. Amylene hydrate eliminated unchanged through lungs and kidney. Detoxification and elimination delayed in presence of liver or renal disease. Exogenous glycuronic acid does not hasten destruction.

PREPARATION

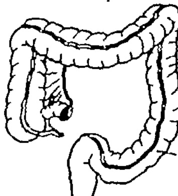
Crystals. Packed in sealed dark ampules available for local application or intravenous use.

Avertin Fluid—Clear somewhat amber heavy fluid, packed in dark bottle. Specific gravity 1.4 at 20°C., sweet, camphor-like odor. Amylene hydrate volatilizes causing precipitation of crystals.



ADMINISTRATION

Used rectally as basal anesthetic (hypnotic). Also used locally as an antispasmodic, particularly in ureteral spasm. When used intravenously it causes short, variable action, followed by prolonged hypnosis. Not suitable orally because of irritation to mucous membranes and decomposition as it passes through stomach.

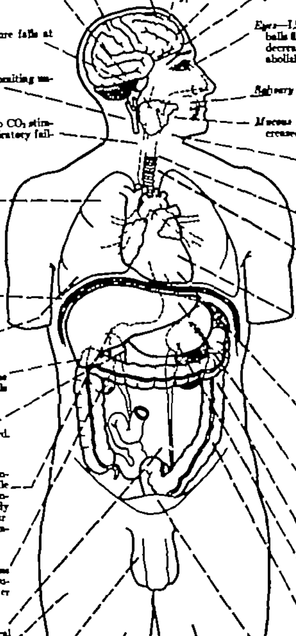


Absorption—Variable—80% absorbed from colon in first 10 minutes; 60% absorbed in first 20 minutes; 95% absorbed in first 25 minutes. None absorbed from small bowel unless ileocecal valve is patent. Absorbed from small intestine more rapidly than large. Onset of hypnosis more rapid if valve is patent. Solutions reach cecum shortly after administration. Non-irritating to mucosa unless decomposed. May cause proctitis following repeated administration.

Duration of Hypnosis—With 80 mgm. per kilo, 25% last less than 1 hour; average duration 2½ hours. Gradual emergence with drowsiness. Excitement follows in post-operative period due to presence of pain.

Blood Concentration—6 to 10 mgm. per 100 cc. of blood results in sleep. Awakening occurs when drug concentration has fallen to 2 to 3 mgm. per 100 cc.

Tissues—Concentration in the heart parallels blood, lipoid and nervous tissue absorb it rapidly and contain it after disappearance from blood, kidney may contain as much as nerve tissue. Cumulative effect follows repeated administration.


Cortex—Depressed. Lower cortical afferent pathways intact. Not an analgesic. Painful stimuli rouse patient in light hypnosis.
Temperature Regulating Center—Depressed. Body temperature falls.
Cough Center—Completely depressed by massive doses only. Reflex present, partly active even in deep hypnosis.
Vasomotor Center—Depressed. Blood pressure falls at onset of hypnosis.
Vomiting Center—Depressed. Nausea and vomiting uncommon.
Respiratory Center—Depressed. Threshold to CO_2 stimulation raised. Overdosage results in respiratory failure.
Lungs—Slight increase in respiratory rate and decrease in amplitude of respiratory movements resulting in a decreased minute volume exchange. Hering-Breuer reflex remains active. No effect on alveoli. Bronchial musculature relaxed. Bronchial cough reflex remains active.
Diaphragm—Movements decreased in deep hypnosis.
Metabolism—Decreased on average of 18%.
Adrenal—No significant effect. Epinephrine content unchanged. Necrosis of adrenals in overdosage reported.
Gallbladder—Volume of bile flow increased. Bilirubin output unchanged.
Liver—Excretion of bromsulphalein impaired. Glycogen depleted. Output of bile salts reduced. Drug detoxified here by conjugation with glycuronic acid. Cloudy swelling only pathological change occurring (never like chloroform). Hepatitis uncommon.
Kidney—Anuria or oliguria during narcosis followed by polyuria afterward. Conjugated product eliminated in urine. Water diuresis normal after narcosis.
Ureters—Relaxation of muscle follows local application.
Nerves—Superficial and deep reflexes remain active in mild hypnosis. Disappear after large dose in deep hypnosis.
Sphincters—Not relaxed except in deep hypnosis. No irritation of rectum unless drug is decomposed or by repeated use.
Body Temperature—Falls due to decreased metabolic rate, depression of center and increased heat loss due to relaxation of skin vessels.
Intracranial Pressure—Decreased if no anoxia is present or during hypotension. Unchanged otherwise. Concentration in spinal fluid one-half that of blood. Spinal fluid pressure decreased.
Pial Vessels—Constricted.
Hypothalamus—Depressed.
Eyes—Lid reflex disappears. Pupils constricted. Eyeballs fixed or movements sluggish. Intraocular tension decreased. Tear secretion reduced. Corneal reflex abolished in deep hypnosis.
Salivary Glands—Depressed. No secretion of mucus.
Mucous Membranes—Not affected. Ciliary activity decreased. Mucus secretion, slight or abolished.
Pharynx—"Gag" reflex not abolished. Tongue sufficiently relaxed to cause obstruction during narcosis. Trace of amylene hydrate in breath.
Thyroid—Resistance to drug increased by administration of thyroxin 24 hours prior to administration of drug.
Larynx—Cough reflex obtunded but not abolished.
Heart—Rate increased, cardiac output decreased. Rhythm slightly changed. EKG changes are insignificant. Large doses depress myocardium and decrease cardiac output, dilatation of coronaries in perfused heart. Does not sensitize heart to epinephrine.
Blood Pressure—Changes occur early (15 min. average). Decrease of 20% or more due to depression of vasomotor center and peripheral vascular dilatation. Systolic falls, diastolic little changed.
Venous Pressure—Decreased. May increase in deep hypnosis.
Spleen—Effects not studied. Probably constricted.
Stomach—Motility decreased or abolished by large doses.
Intestines—Motility reduced or abolished by large doses.
Uterus—Contractions of pregnant uterus decreased in force and frequency. Atony and relaxation follows large doses. Drug passes through placenta to fetus depressing respiration. Recovery of infant delayed as long as one week.
Skin—Temperature increased due to dilatation of skin vessels. Bromides recovered in sweat. Drug in alcoholic solution absorbed through skin.
Skeletal Muscles—Relaxed with large doses.

Total Blood Volume—Decreased.

Red Blood Cells—Increased in number. Total hemoglobin increased. No change in morphology of cells. Sedimentation rate decreased.

Leukocytes—Total increased. Polymorphonuclears increased relatively and absolutely in first 24 hours. No change in morphology. Phagocytosis decreased in deep narcosis.

Platelets—Decreased as much as 75% after 30 minutes of narcosis.

Oxygen Capacity—Slightly increased due to hemoconcentration. Oxygen content unchanged in arterial blood unless respiratory depression occurs.

Carbon Dioxide—Total content increased.

Carbon Dioxide Combining Power—Decreased. Returns to normal within 48 hours. Total base decreased. Bicarbonate increased at first, decreased after 30 minutes. pH increases 0.1 to 0.2 units during narcosis.

Bleeding Time—Decreased due to hypotension. Capillary tone minimal.

Clotting Time—Increased as much as three minutes.

Plasma Volume—Decreased.

Calcium—Unchanged.

Bicarbonate—Reduced.

Phosphates—Total phosphates increased during recovery.

Chlorides—Unchanged.

Glucose—30% increase within first 30 minutes with a continued rise thereafter. Derived from liver glycogen which is depleted.

Non-protein Nitrogen—Increased during narcosis. Returns to normal within 24 hours. Gradually falls after recovery.

Urea—Decreased during narcosis. Returns to pre-narcotic level during recovery.

Lipoids—No significant change. Slight increase in total cholesterol. No change in cholesterol ester content.

Bile Salts and Bilirubin—Slightly decreased plasma level.

Ketones—Appear after narcosis.

Pathology—No definite pathological changes ascribable to drug.



URINE

Specific gravity increased. Volume decreased during and increased after narcosis. Total 24-hour volume decreased. Non-protein nitrogen decreased during and increased after narcosis. Phosphates increased, maximum in 6 hours. Albumin present in 60% of cases. Detoxified product excreted in urine.

USES

(1) As "basal narcosis" (in conjunction with other forms of anesthesia—inhalation or regional) for apprehensive patients.
(2) To control hyperirritable states of central nervous system manifested by convulsions.
(3) As bronchodilator in asthmatic states.
(4) For intracranial surgery.
(5) As an antispasmodic.

ADVANTAGES

(1) Reduces metabolic rate and reflex irritability.
(2) Rapid onset on induction of narcosis.
(3) Gradual recovery resulting in prolonged amnesia.
(4) May be administered at bedside to allay preoperative apprehension.
(5) Eliminates excitement during induction of inhalation anesthetic.
(6) Non-irritating to respiratory tract.
(7) Post-operative nausea and vomiting decreased.
(8) Reduces amount of inhalation anesthetic.
(9) Reduces intracranial pressure.

CONTRAINDICATIONS

(1) Hepatic or renal disease.
(2) Any "toxemia" or sepsis or acidosis from any cause.
(3) Shock or other forms of hypotension.
(4) Dehydration.
(5) Low basal metabolic rate (hypothyroidism).
(6) Chronic pulmonary diseases.
(7) Enteritis, colitis, neoplasms of colon.
(8) Old age.
(9) Anemias.
(10) Chronic alcohol addicts.

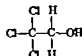
DISADVANTAGES

(1) Non-controllable—once given dose is administered it cannot be retrieved.
(2) Must be detoxified for elimination.
(3) Dose difficult to estimate due to variations in susceptibility and absorption from rectum.
(4) Not an analgesic—supplemental anesthetic agent necessary to complete surgical procedures.
(5) Respiratory depression common.
(6) Hypotension frequent.
(7) Repeated doses result in cumulative effects.
(8) Laryngeal and pharyngeal reflex not abolished.
(9) Requires constant attendance by expert individual during period of narcosis.
(10) Not chemically stable—decomposed solutions cause rectal and colonic irritation.

TRICHLORETHANOL

HISTORY—Introduced by Kulz in 1882 Molitor reinvestigated its pharmacological properties in 1937 Used clinically by Wood in the United States in 1938. Also known as Ethapon.

CHEMICAL PROPERTIES—Clear colorless liquid specific gravity 1.55 (20°C) 8.8% solubility in water at 20°C boiling point 151°C. at 737 mm Hg Not flammable Sweet smelling, stable. Decomposes at temperatures above 40°C. Onset of narcosis irregular Duration one to five hours. Amylene hydrate not required Chemical structure as follows



Cortex—Depressed. Response similar to tribromethanol.

Temperature Regulating Center—Depressed. Body temperature falls.

Vasomotor Center—Depressed. Causes fall in blood pressure similar to tribromethanol.

Respiratory Center—Depressed. Respiration fails before circulation. Similar to tribromethanol.

Vomiting Center—Not stimulated. Nausea and vomiting uncommon.

Cough Center—Remains active Depressed in deep hypnosis.

Lungs—Respiratory rate and minute volume exchange decreased. Regular rhythm Not eliminated by lungs. Nonirritating to lungs.

Bronchi—Dilated

Metabolism—Decreased.

Liver—Detoxified by conjugation with glycuronic acid. Glycogen decreased mild hyperglycemia results Function not decreased (bromsulphalein excretion) No pathological changes ascribable to drug.

Kidney—No nitrogen retention No pathological changes ascribable to drug.

Rectum—Administered in 3% aqueous solution Non-irritating to mucosa in this strength.

Sphincters—Not relaxed except in deep hypnosis.

Eyes—Pupils constricted. Movements sluggish. Similar to tribromethanol.

Mucous Membranes—Not affected. Slight or no mucus secretions.

Salivary Glands—No increase in secretion. Depressed during narcosis.

Pharynx—"Gag" reflex not abolished. Tongue may relax sufficiently to cause obstruction in deep hypnosis.

Larynx—Laryngeal reflex sluggish but not abolished. Intubations and bronchoscopic examinations difficult.

Heart—Rate increased. Rhythm not changed.

Blood Pressure—Decreased as much as 30% due to central depression shortly after onset of hypnosis.

Spleen—Effects not known.

Gastrointestinal Tract—Similar to tribromethanol.

Skeletal Muscles—Muscle relaxation inadequate for surgery

Skin—Irritated if applied locally undiluted.

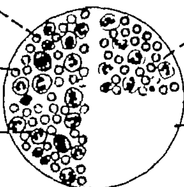
Reflexes—Not completely abolished supplemental agent required for surgery

Trichlorethanol differs from tribromethanol in having three chlorine atoms in place of the bromine atoms. Pharmacologically they are similar Trichlorethanol possesses a somewhat wider margin of safety but a milder potency

Oxygen Content—No decrease in arterial blood.

Glucose—Slight rise.

Bleeding Time—Unchanged.



Carbon Dioxide Combining Power—Decreased.

Clotting Time—Unchanged.

USES

Same as for tribromethanol.

INDICATIONS

Same as for tribromethanol.

METHODS OF ADMINISTRATION

Rectally—Same as for avertin.
Intravenously—Not useful or recommended.
Orally—Similar to tribromethanol—not suitable

CONTRAINDICATIONS

Same as for tribromethanol.

ADVANTAGES

Similar to tribromethanol in comparison to other hypnotic drugs. Superior to avertin as follows:

(1) It is less expensive
(2) It is somewhat more stable chemically
(3) It does not require amylene hydrate or other vehicle as a solvent.

Dose—100-125 mgm. per kilogram in a 3% solution (aqueous) rectally

Onset of Hypnosis—Approximately 10 minutes after administration.

Duration of Hypnosis—One to two hours when administered rectally

Elimination—Detoxified by conjugation with glycuronic acid. Usually eliminated within six hours.

DISADVANTAGES

Same as for tribromethanol. Inferior to tribromethanol in the following ways:

(1) It is less potent.
(2) Its response and duration of action are more variable.
(3) Respiratory depression often more profound.
(4) Dose is estimated with greater difficulty
(5) Duration of hypnosis shorter

CHLORAL (TRICHLORACETALDEHYDE)

HISTORY—First prepared by Leibig in 1832. Composition determined by Dumas in 1834 Introduced by Leibreich. First drug to be used for intravenous anesthesia by P Oré in 1875 in France (Lyons)

CHEMISTRY—Made by chlorinating and oxidizing ethyl alcohol with chlorine. Forms a hydrate with water

PROPERTIES

Physical—Clear colorless, caustic liquid with a pungent disagreeable odor Boils at 98° S.G 1.506 at 25°C.

Chemical—Forms hydrate with water which melts at 57° and boils at 96° Both derivatives very soluble in alcohol, water and ether Forms alcoholate with ethyl alcohol and chloralose with glucose Solutions are antiseptic. (Included in U.S.P XIII.)

Cortex—Depressed. Small doses cause sedation or hypnosis; large doses basal narcosis. Possesses no analgesic action. Hypnotic doses produce sleep from which patient can be awakened.

Temperature Regulating Center—Depressed by massive doses. No effect in hypnotic doses.

Respiratory Center—Sedative and hypnotic doses have no remarkable effect. Basal narcotic and toxic doses depress. Respiration ceases before circulation.

Lungs—No effect. Respiration depressed with basal narcotic doses. Respiratory exchange depressed during hypnosis.

Bronchi—No significant action. Relaxed after basal narcotic dose.

Metabolism—Depressed if sleep ensues.

Liver—Not affected by hypnotic doses. Hepatitis may follow repeated administration or toxic doses. Liver glycogen mobilized after massive doses causing hyperglycemia.

Kidney—Urine flow decreased during basal narcosis. By-product of detoxification (urochloralic acid) eliminated by kidney Albuminuria after toxic doses. Reducing substance eliminated into the urine often mistaken for glucose.

Elimination—Detoxified in liver by conjugation with glycuronic acid to form urochloralic acid (usual dose excreted in 2 to 18 hours)

Skin—Locally irritating. Cutaneous vessels dilated Skin eruptions may follow use as hypnotic

Vasomotor Center—No effect with sedative and hypnotic doses. May be depressed after massive doses.

Eye—Pupils constricted in deep hypnosis. Reflexes and eye ball movements abolished.

Pharynx—Locally irritating.

Larynx—No effect. Laryngeal reflex obtunded but not completely abolished in deep hypnosis.

Salivary Glands—Stimulated by oral ingestion.

Heart—Hypnotic doses cause no effect. Massive doses depress myocardium. No notable effect on cardiac rhythm during sedation or hypnosis.

Blood Pressure—No effect. Reduced if elevated from psychic stimulation. Toxic doses may depress vasomotor center

Stomach—Absorbed from stomach in part. Irritating to mucosa of gastrointestinal tract. Causes hyperemia, nausea and vomiting from local irritation.

Intestines—Rapidly absorbed from intestinal tract. Rapidly absorbed from colon in rectal administration.

Body Temperature—Slightly lowered due to heat loss through skin.

Reflexes—Unchanged during hypnosis. Depressed during basal narcosis.

CLINICAL USES

(1) As hypnotic alone or in combination with bromides.
(2) As an anti-convulsant (tetanus, strychnine poisoning, rabies, etc)
(3) As basal hypnotic and narcotic in pediatrics, surgery and medicine

Onset of Hypnosis—Rectally—10 to 15 minutes. Orally 15 to 30 minutes. Lasts 5 to 8 hours

After Effects—Very few after effects upon recovery Tolerance uncommon Addiction unlikely No potentiation if administered with ethyl alcohol

ADMINISTRATION

Orally—For mild sedation 0.5 to 1 gm. For hypnosis 1 to 2 gm.

Rectally—For basal narcosis 2 to 4 gm. Not recommended.

Intravenously—Not used.

LESSER KNOWN ALCOHOLS AND ALDEHYDES

	Amylene Hydrate	Pentyn-ol	Chlorbutanol	Butyl Chloral Hydrate
History	Studied by Harnoch and Meyer in 1894.	Introduced in 1951—Shering Corp.	—	Introduced by Liebreich in 1871. Investigated by Aldrich 1918.
Synonyms	*Tertiary amyl alcohol.* Tertiary pentanol.	*Dormison.*	*Chloretone.* Acetone chloroform. Methaform.	"*Croton chloral hydrate.*
Chemical Name	Dimethyl ethyl carbinol.	3,methyl pentyn-ol 3	Chlorobutol.	Trichlorobutyraldehyde.
Formula	$C_2H_5(C)(CH_3)_2OH$	$CH \equiv C-C(CH_3)(OH)-CH_2-CH_3$	$(CCl_3)(C)(CH_3)_2OH$	$CH_3CHCl-CCl_2CHO$
Properties	Colorless volatile liquid B.P 102°C. Soluble 1 in 8 H_2O	An unsaturated triple bonded aliphatic alcohol.	Colorless crystals with camphor like odor M.P 97°C. 1 gm. in 125 CC. H_2O	Crystalline white powder, pungent odor acrid taste 1 in 50 H_2O. Melts at 78°C.
Absorption	From gastro-intestinal tract. Orally 1–2 cc. I.M. 2–4 cc.	From gastro-intestinal tract.	From mucous membrane of G.I. tract.	From gastro-intestinal tract orally and rectally
Excretion	Into urine May be conjugated in part in liver	Into urine Rapidly eliminated	Non-volatile. Excreted into urine or detoxified.	Non-volatile Excreted into the urine or detoxified.
Systemic Effect	Mild hypnotic.	Mild hypnotic. More potent than amylene hydrate	Depressant used for hypnotic purposes.	Similar to chloral
Toxicity	Excessive doses depress heart.	Low toxicity	Large doses depress respiration.	Similar to chloral.
Uses	As hypnotic. Solvent for amylene hydrate Plays a minor role in hypnosis.	As a hypnotic orally	Antispasmodic, sedative preservative for parenteral solutions.	As a hypnotic.
Doses	1–4 cc. orally 4–8 cc. rectally	250–500 mgm. orally	0.3–1 gm. orally	0.3 1 gm. orally
Analgesic Effects	None	None	Possesses some local anesthetic effect.	Mild analgesic action.
Remarks	Between chloral and paraldehyde in potency	Low toxicity Non-cumulative. Antagonized by caffeine.	Depress smooth muscle of G.I. tract. Inhalant in respiratory infections.	May be used externally More powerful and shorter acting th-- chloral.

THE SULPHONE METHANES

The sulphone methanes have been employed for sedation and hypnosis, but because of their feeble action and their tendency to produce cumulative effects are no longer employed Three of the most important derivatives in this group possess the following properties.

Name	Sulphonal	Trional	Tetronal
History	Introduced by Bauman and Kast in 1888.	Same.	Same.
Properties	Sulphonmethane White bitter powder—slightly soluble in water (1 in 336), melts at 124–126°	Diethyl sulphone ethyl methyl methane Whit bitter powder Colorless, odorless crystalline scales. Poorly soluble in water	Diethyl sulphone diethyl methane Bitter white powder Poorly soluble in water
Action	Hypnotic but not analgesic. Absorbed slowly Onset one to four hrs. Duration one to five hrs.	Hypnotic but not analgesic.	Hypnotic but not analgesic.
Elimination	Cumulative action results Excreted partly as ethyl sulphonic acid and partly unchanged in urine Excreted slowly	More rapidly absorbed and therefore more prompt in its action than sulphonal. Excreted slowly int urine. Cumulative action follows repeated administration.	Slower in onset than sulphonal because of slower absorption. Excreted slowly into urine. Cumulative action follows repeated administration.
Toxic Effects	Large doses depress respiration and circulation		Large doses depress circulation and respiration.
Dose	Dose 1 gm. orally	Dose 1 gm. orally	Dose 1 gm.
Use	As sedative and hypnotic. Used as a hypnotic formerly Rarely used today	As a sedative and hypnotic Used as a hypnotic formerly Rarely used today	As a sedative and hypnotic. Same as sulphonal but slower in action because it is less soluble in water

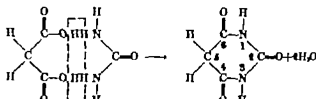
SECTION IX BARBITURATES AND OTHER NONVOLATILE AGENTS

BARBITURATES

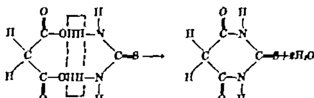
HISTORY—Barbital prepared by Fischer and Von Mering in 1903 phenobarbital by Hoerlein in 1911 Shonle began to *prepare higher molecular weight derivatives in 1916 Since then many chemists have added new compounds.*

CHEMISTRY OF BARBITURATES

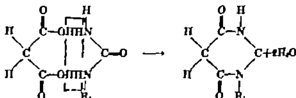
Chemistry—Barbiturates are cyclic ureides composed of a pyrimidine nucleus resulting from a condensation of urea and malonic acid. The resulting malonyl urea (barbituric acid) is non-hypnotic Replacement of the two hydrogens on carbon 5 by various radicals produces a myriad of central nervous system depressants.



Thiobarbiturates—Made by condensing malonic acid with thiourea. Possess similar configuration to barbituric acid except one oxygen atom is replaced by sulphur Forms salts which are yellow hygroscopic powders with pleasant, aromatic odor Chemical properties as similar to barbiturates. Pentothal in this group.



N-substituted barbiturates. Made by condensing malonic acid with substituted ureas (methyl urea, ethyl urea, etc) Form salts which are white powders chemically similar to barbiturates. Evipal is in this group.



Chemical Properties—Are white powders. Average melting point between 100° to 200°C. All are weak acids soluble in organic solvents and poorly soluble in water Dissolve in bases to give salts; salts poorly soluble in organic solvents but soluble in water Sodium salts most common; aqueous solutions of sodium salts are alkaline having between pH 9–10 solutions of barbiturates unstable; hydrolyze on standing, or if boiled. Solutions for intravenous use prepared from drug in sealed, sterile ampules.



TYPES OF BARBITURATES

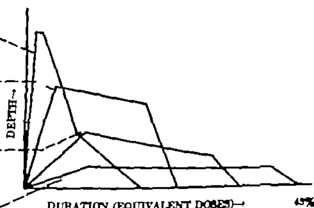
Over 1100 barbiturates are theoretically possible Hundreds have been prepared The clinically useful barbiturates, N-substituted barbiturates, and thiobarbiturates may be divided into four groups as follows:

Ultra Short Acting—Pronounced, intense hypnotic action, rapidly induced, of brief duration, followed by mild hypnosis or heavy sedation. Useful for abolition of consciousness during surgical procedures. Destroyed by liver Most effective intravenously

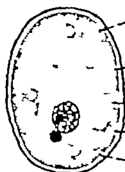
Short Acting—Moderate hypnotic action quickly induced (30 to 40 minutes) for four to eight hours followed by slight or no sedative effect (hangover) Useful for inducing sleep by oral use Less commonly by intramuscular or intravenous injection. Rapidly detoxified by liver

Intermediate Acting—Intense sedative action or mild hypnotic action Onset gradual one to two hours lasting eight to twelve hours followed by slight sedative effect Partly destroyed in liver Used orally or intramuscularly

Long Acting—Mild sedative action with little or no hypnotic effect in therapeutic doses. Onset and recovery gradual and action is sustained over many hours. Little or no destruction by liver in therapeutic doses Eliminated in urine Partly detoxified when massive doses are administered. Used orally or intramuscularly



BIOLOGICAL EFFECTS



Surface Tension—Surface tension of water lowered in vitro. Degree of lowering parallels narcotic potency. Possible similar effect on cell membrane postulated—causing narcosis. Rate and degrees of hydrolysis in vitro does not parallel and is not related to narcotic efficacy.

Adsorption—Readily adsorbed on activated surfaces such as ash-free charcoal, similar action may occur at cell membrane which decreases permeability and alters metabolism, which in turn causes narcosis.

Lipoid Solubility—Lipoid-water solubility ratios parallel narcotic potency. Behave like aliphatic compounds. Follow Overton-Meyer rule.

Tissue Oxidation—Reduced in vitro. Dehydrogenases inactivated. Oxidases not affected.

Permeability of Cell—Decreased. May cause metabolic changes which result in narcosis.

Effects—Barbiturates are central nervous system depressants. Possess no analgesic action. Cause psychic sedation, sleep, deep hypnosis or anesthesia. Results vary with type drug, dose mode of administration, rat of absorption, rate of destruction or elimination and susceptibility of the subject to drug.

METHODS OF ADMINISTRATION AND USES

1. *Oral*. For sedation and hypnosis. Last four t eight hours or more Rapidly absorbed from small intestine when administered orally Slight absorption from stomach, unless massive doses are given.

2. *Rectal*. For sedation, sleep or basal hypnosis. Surgical anesthesia obtained with complemental inhalation anesthesia or regional block. Hypnosis lasts variable period of 4 hours more or less.

3. *Intraperitoneal*—For anesthesia in animals. Rapid and prolonged action of four or five hours duration.

4. *Intravenous*—One dose usually about 1 gram of an ultra-short acting drug administered rapidly in from 5% to 10% solution yields immediate deep hypnosis to complete anesthesia lasting for 20 to 30 minut periods. Followed by sleep upon reacting. Cumulative action forbids repeating dose

Absorption—Long, intermediate and short acting drugs are absorbed rapidly from small intestine when given by oral rout and from large bowel by rectal route Some absorption from stomach particularly when massive doses are given. Ultra short acting derivatives may be ineffective because they are rapidly destroyed unless injected directly into blood stream.

Efficiency—Measured by the minimum effective dose In order of increase barbital, phenobarbital, amytal, neonal, nembutal, ortal.

Toxicity—Measured by the minimum lethal dose Does not parallel efficiency In order of increase: barbital, neonal, sandoptal, dial, amytal, phenobarbital.

Margin of Safety—Ratio between the effective dose and toxic dose. In order of increase phenobarbital, barbital, amytal, nembutal, dial, neonal, sandoptal.

Synergistic Action—Efficacy of barbiturates increases if used in combination with analgesics such as pyramidon, antipyrine acetyl salicylic acid, codeine amidone demerol, etc. Do not potentiat analgesic action of these drugs however

The two hydrogens on carbon 5 may be substituted by aliphatic, aromatic or alicyclic radicals to yield compounds many of which possess hypnotic and sedative properties. Potency increases as molecular weight increases. When total number of carbons on both radicals begins to exceed 8 toxicity increases out of proportion to potency. Halogenation, unsaturation and branching of chain increase the potency, intensity and duration of action. Compounds possessing aliphatic radicals derived from secondary alcohols are more potent than those derived from primary.

Radical on Carbon 5	Radical on Carbon 5'	Result
Short straight chain (ethyl)	Short straight chain (ethyl)	Long acting compound of low potency and toxicity (barbital)
Short straight chain (ethyl)	Long straight chain (butyl)	Increased potency, shortened duration, intermediate acting or short acting derivative (butisol)
Short straight chain (ethyl)	Short branched chain (isopropyl)	Intermediate acting derivative (ipral)
Short straight chain (ethyl)	Long branched chained radical derived from a primary alcohol (isoamyl)	Intermediate to short acting derivative (amytal)
Short straight chain (ethyl)	Long aliphatic radical derived from secondary alcohol (sec-methyl-butyl)	Short acting, high potency derivative (pentobarbital)
Short straight chain (ethyl)	Aromatic (phenyl)	Long acting, low potency derivative (phenobarbital)
Aromatic (phenyl)	Aromatic (phenyl)	No narcotic effect
Short unsaturated (allyl)	*Short unsaturated (allyl)*	*Intermediate and short acting derivative of moderate intensity (dial)*
Short straight chain with unsaturated linkage (vinyl)	Long straight chain	Short acting, high potency derivative (vinyl barbital)
Short unsaturated (allyl)	Long aliphatic derived from secondary alcohol (sec-methyl-butyl)	Short acting, high potency derivative (seconal)
Short straight chain (ethyl)	Cyclic saturated	Short acting, high potency derivative
Short straight chain (methyl)	*Unsaturated cyclic (cyclo-hexenyl)*	*Ultra short acting derivative of high potency (evipal)*
Straight chain (butyl)	Unsaturated straight with halogens (brom-allyl)	Short or ultra short acting derivative of high potency (pernoston)

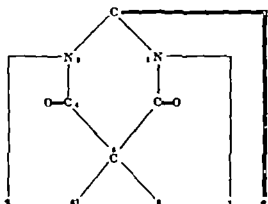
DETOXIFICATION OR ELIMINATION—Ultra short-acting and short-acting compounds are destroyed in the body probably in the liver. Destruction results in disruption of the malonyl urea ring. Degradation products may appear in the urine, particularly if large doses are administered. Intermediate-acting derivatives are partly destroyed in the body and partly excreted unchanged in urine.

Long-acting drugs are eliminated almost entirely unchanged in the urine. N-substituted derivatives (evipal) and the thiobarbiturates (pentothal) of higher molecular weight are not recovered in urine but are probably detoxified by the liver.

Halogenated unsaturated substituted barbiturates are eliminated with alterations in side chains with little break down of ring structure. Short acting drugs cause prolonged action when hepatic dysfunction is present, influenced little or none by renal insufficiency. Prolonged hypnosis results when long acting barbiturates are administered in presence of renal insufficiency, but as a rule not affected by presence of hepatic insufficiency.

PHARMACOLOGY OF BARBITURATES

Barbituric acid is a six-membered ring possessing the pyrimidine nucleus. The two hydrogen atoms on carbon 5 when substituted by aliphatic, cyclic, aromatic and other radicals yield numerous derivatives possessing hypnotic powers. The hydrogen atoms on either nitrogen atoms yield compounds called N-substituted barbiturates. The oxygen atoms on carbon 4 and 6 remain intact. Cyclic radical embodying carbon 5 results in spirobarbiturates.



Name	Fate	Action and Uses	3	5'	5	1	2
Barbital (U.S.P.) Medinal	Mostly unchanged, eliminated five to seven days in urine	Long-acting sedative	H	Ethyl	Ethyl	Na	O
Phenobarbital (U.S.P.) Luminal (proprietary)	Eliminated unchanged, recovered in urine	Long-acting sedative	H	Phenyl	Ethyl	N	O
Ipral (proprietary)	Partly destroyed and partly recovered in urine	Intermediate sedative	H	Ethyl	Isopropyl	Na Ca	O
Neonal (proprietary)	Partly destroyed and partly recovered in urine	Intermediate sedative	H	Ethyl	n-Butyl	H	O
Dial (proprietary)	Mostly destroyed, some in urine	Intermediate sedative	H	Allyl	Allyl	H	O
Alurate (proprietary)	Small part in urine, mostly destroyed	Intermediat hypnotic	H	Allyl	Isopropyl	Na	O
Sandoptal (proprietary)	Destroyed, none in urine	Short-acting hypnotic	H	Allyl	Isobutyl	H	O
Ortal (proprietary)	Destroyed, none in urine	Short-acting hypnotic	H	Ethyl	n-Hexyl	Na	O
Amytal (proprietary)	Destroyed, less than 3% in urine	Short-acting hypnotic	H	Ethyl	Isoamyl	Na	O
Pentobarbital (U.S.P.) Nembutal (proprietary)	Destroyed, none in urine	Short-acting hypnotic	H	Ethyl	1,Methyl butyl	Na	O
Phanodorn (proprietary)	Destroyed, less than 3% in urine	Short-acting hypnotic	H	Ethyl	Cyclo hexenyl	H	O
Pernoston (proprietary)	Destroyed, none in urine	Short-acting basal hypnotic	H	β-brom allyl	Butyl	H	O
Nostal (proprietary)	Destroyed, none in urine	Short-acting hypnotic	H	β-brom allyl	Isopropyl	H	O
Evipal, Evipan Hexobarbitone	Destroyed, none in urine	Ultra short-acting basal hypnotic	CH_3	Methyl	Cyclo hexenyl	Na	O
Pentothal (proprietary) Thiopentone Thiopental	Destroyed, none in urine	Ultra short-acting basal hypnotic	H	Ethyl	1,Methyl butyl	Na	S
Seconal (proprietary)	Destroyed, none in urine	Hypnotic	H	Allyl	1,Methyl butyl	Na	O
Delvinal Vinbarbital (proprietary)	Destroyed, none in urine	Hypnotic	H	Ethyl	1,Methyl 1,Butenyl	Na	O
Mebaral (proprietary)	Destroyed	Hypnotic anti-convulsant	CH_3	Ethyl	Phenyl	N	O
Butisol (proprietary)	Partly destroyed	Sedative and mildly hypnotic	H	Ethyl	Sec. butyl	Na	O
Surital (proprietary)	Destroyed, none in urine	Basal hypnotic	H	Methyl butyl	Allyl	Na	S
Thioethamyl (proprietary)	Destroyed, none in urine	Basal hypnotic	H	Ethyl	Isoamyl	Na	S
Kemithal (proprietary)	Destroyed, none in urine	Basal hypnotic	H	Allyl	Cyclo hexenyl	Na	S

A progressive depression of the central nervous system may be observed when many barbiturates are administered slowly intravenously. The phylogenetically newer portions of the cerebrospinal axis are affected first, giving rise to phenomenon akin to the planes and stages of narcosis observed in the case of aliphatic general anesthetics. Rapid administration of short and ultra short-acting barbiturates causes a telescoping and non-appearance of the following signs

Stage	Site of Depression	Characteristics	Eye	Respiration	Circulation
I. Clouded consciousness	Cortex. Slight to moderate depression.	Euphoria. Loss of discrimination to loss of appreciation of environment. Loss of coordination of motor activity	Pupil size reaction to light and corneal reflex unchanged.	No significant change	No significant change.
II. Hypersensitive	Cortex—complete depression. Subcortex—slight depression, particularly subthalamic and motor nuclei.	Motor activity and excitement absent. Increased sensitivity to external stimuli causes exaggerated movement.	Roving eyeball. Corneal reflex becomes sluggish. Pupil size and reaction to light unaltered.	No significant change	No significant change.
III. Basal Narcosis a	Subcortical and diencephalic structures (thalamus, hypothalamus and basal ganglia depressed)	Sensitivity to external stimuli decreased. Response to pain diminished.	May oscillate or be fixed. Reaction to light disappears. Lid reflex depressed.	Mildly depressed.	Slight increase in pulse rate. Blood pressure changes slightly
b	Partial depression of midbrain.	Pain excites changes in pupils and respiratory rate. Pupils remain constricted.	Usually fixed eyeball. Reaction to light gone. Corneal reflex depressed.	Depressed.	Increased pulse rate. Blood pressure may decrease
c	Complete depression of midbrain and beginning to moderate depression of medulla.	Pain no longer affects pupils or respiration.	Fixed. Reaction to light gone. Corneal reflex depressed.	Marked depression or apnea.	Increased pulse rate Blood pressure may decrease.
IV. Medullary depression	Depression of medulla.	Depressed respiration. Circulatory collapse Muscles relaxed	Pupils dilate	Apnea.	Blood pressure falls.

TREATMENT OF MASSIVE OVERDOSAGE

SYMPTOMS—Coma, hypothermia early, fever later, sluggish or absent reflexes, respiratory depression and gradual appearance of circulatory collapse

TREATMENT

1. Institute adequate pulmonary ventilation—airway, oxygen, assisted or artificial respiration
2. Remove stomach contents by aspiration or lavage (if orally ingested)
3. Support circulation *if depression is present by administering fluids, blood, etc.*
4. Promote diuresis.
5. Lavage colon to remove drug excreted into large bowel.
6. Administer analeptic drug. Picrotoxin 1 mgm. per minute intravenously until patient begins to stir
7. Administer antibiotics to prevent pulmonary complications.

GENERAL REACTIONS OF LONG AND INTERMEDIATE ACTING BARBITURATES

Cortex—Spontaneous activity inhibited. Small doses cause sedation large doses hypnosis. Sleep is dreamless and resembles natural sleep. Lower afferent pathways remain intact and transmit impulses to cortex. Pain stimuli arouse subject and induce delirium. Restlessness often follows recovery from deep hypnosis.

Temperature Regulating Center—No effect from sedative doses. Depressed by massive doses.

Cough Center—No effect. Massive doses depress.

Vomiting Center—Depressed. Control nausea in sedative doses.

Vagus Center—Cardiac portion of vagus depressed; respiratory portion remains active

Respiratory Center—No effect by hypnotic and sedative doses. Depressed by large doses. Sensitivity to carbon dioxide decreased.

Vasomotor Center—No significant effect in sedative and hypnotic doses. Directly depressed by massive doses. Blood pressure falls.

Carotid-aortic Chemoreceptors—No notable effect. Reflexly maintain respiration in overdosage Depressed by massive doses.

Lungs—Minute volume exchange decreased due to psychic sedation. Respiratory rate may increase; amplitude decreases with large doses. Hering-Breuer reflex remains active. Massive doses cause central respiratory depression and respiratory paralysis.

Metabolism—No significant change in basal metabolic rate Decreased by massive doses. Reduction in hyperthyroidism due t sedative effect.

Liver—Hypnotic doses have no effect. Massive doses decrease function (dye test) Glycogen content decreased by massive doses.

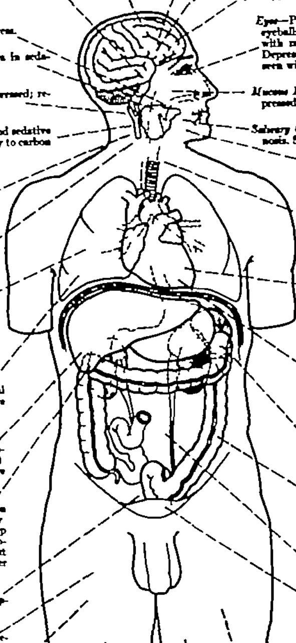
Kidney—Hypnotic doses have no effect on renal function. Oliguria followed by polyuria from decreased water diuresis in deep hypnosis. Probably due t action on hypothalamic pituitary system. Urinary output returns to normal within 6 to 24 hours after recovery

Sphincters—Unaffected by sedative and hypnotic doses Relaxed with massive doses.

Reflexes—Mild depression of superficial reflexes. Deep reflexes exaggerated in hypnosis. All are depressed in deep hypnosis.

Skeletal Muscles—Tone unchanged with sedative doses; relaxed in deep hypnosis from massive doses Convulsions controlled by intravenous doses by action on cortex (phenobarbital) subcortical structures and cord. Glycogen content unchanged

Skin—Temperature increases from peripheral vasodilatation. Rashes due to sensitivity or prolonged use of some drugs not uncommon.



Hypothalamus—Depressed thought to be primary site of action.

Cerebral Vessels—Sedative and hypnotic doses cause no change Dilated by large doses.

Intracranial Pressure—Unchanged. Decreased by massive doses, probably secondary to hypotension. Spinal fluid concentration insignificant.

Eyes—Pupils remain in mid-dilatation. Movements of eyeballs remain active with sedative doses. Fixation with massive doses. Corneal reflex remains active. Depressed by massive doses. Constricted pupils often seen with overdosage

Mucous Membranes—Ciliary activity not affected. Depressed by massive doses.

Salivary Glands—Little effect during sedation or hypnosis. Secretions depressed by massive doses.

Pharynx—No effect on "gag" reflex. Reflex absent only in deep hypnosis. Tongue may relax and cause obstruction in deep hypnosis.

Larynx—Laryngeal reflex remains active. May be exaggerated during hypnosis. Stimulation may cause spasm. Absent in very deep hypnosis.

Heart—No notable effect on myocardium. Depressed by massive doses. Rat unchanged *during hypnosis or sedation.* Tachycardia with massive doses. No notable effect on rhythm. Arrythmias of various types with massive doses.

Blood Pressure—No significant effect in hypnotic doses. Massive doses cause hypotension due t depression of vasomotor center and heart. Increased capillary permeability from massive doses.

Spleen—No effect in sedative or hypnotic doses. Dilated in deep hypnosis. Red cell content increases.

Gastrointestinal System—Sedative and hypnotic doses cause an antispasmodic action due to central depression and removal of psychic influences. *Large doses depress* smooth muscle and decrease motility

Pancreas—Secretions unaffected. Blood amylase unchanged.

Uterus—No effect from sedative and hypnotic doses. Contractions and tone decreased by massive doses. Pass through placenta t *fetus* causing respiratory depression. Fetal arterial oxygen content unchanged ordinarily

Body Temperature—Unchanged by sedative and hypnotic doses. Decreased by massive and toxic doses due to reduced metabolism, vasodilatation and depressed activity of heat regulating center

Habituation—Frequent. Tolerance (psychological dependence) and cross *tolerance common. Addiction* (physical dependence) unusual. Withdrawal symptoms unusual. Overdosage from automatism frequent in self medication.

Red Blood Cells—Decrease in number. Increase in cell volume frequent.

Glucose—No significant changes with sedative and hypnotic doses. Elevation with doses which cause deep hypnosis or basal narcosis.

White Cells—No significant changes. Increase after deep hypnosis.

Bleeding Time—Unchanged.

Oxygen Capacity—Not significantly altered. Usually decreased.

Clotting Time—Unchanged.

Carbon Dioxide Content—No change or slight elevation. Increased with massive doses.

Inorganic Ions—No significant changes.

Carbon Dioxide Combining Power—Variable. Slight or no change with sedative and hypnotic doses. Massive doses cause lowering of pH due to accumulation of fixed acids.

Non-protein Nitrogen—No significant changes unless oliguria follows, which causes elevation.

URINE

Output—Decreases during hypnosis and returns to normal within 24 hours.



Water Diuresis—Decreased with return to pre-hypnotic value after deep hypnosis or in toxic doses. *Long* and intermediate acting drugs in therapeutic doses are recovered in urine; *short* and *ultra short-acting* only after massive doses.

PATHOLOGY

No significant or characteristic histological changes ascribable to the drug.

USES

(1) For hypnosis.
(2) To antagonize convulsions from stimulating drugs.
(3) As basal or for pre-anesthetic sedation.
(4) In psychiatric interviews.

ADVANTAGES OVER OTHER HYPNOTICS

(1) Cause few side effects or metabolic disturbances.
(2) No effects on blood forming organs.
(3) Tolerance develops slowly.
(4) Cumulative effects occur slowly.
(5) Sleep resembles natural sleep.
(6) Physical dependence uncommon.

CONTRAINDICATIONS

(1) Hepatic diseases.
(2) Shock-like states.
(3) For analgesia.

DISADVANTAGES

(1) Large doses cause severe respiratory depression.
(2) Non-analgesic.

ULTRA SHORT ACTING BARBITURATES (THIOPENTAL)

SYNONYMS—Pentothal, thionembutal, thiopentobarbital, thiopentone 8064 thiobarbiturate A.

HISTORY—First attempt at *intravenous injection* in man was by Christopher Wren (London, 1657) First attempt at *intravenous anesthesia* by Sigmund Elsholtz in 1665 using an opiate solution. Ore of Lyons, France (1862) produced anesthesia in man using intravenous chloral hydrate. Krawkow in 1905 produced anesthesia with intravenous Hedonal Burkhardt (Germany 1909) described intravenous use of narcotics, ether and chloroform. Noel and Souttor (1913) described intravenous use of paraldehyde Then followed use of magnesium sulphate (Peka Neltzer) alcohol (Naka gawa 1921) Avertin (Kirshner 1929) somnifen (barbiturate) (Germany 1924) pernocton (1927) Amytal (Lundy 1929) Nembutal (Waters 1929)

First successful use of ultra short-acting barbiturate was in Germany by using Evipal (Weese 1933) Thiopental first used experimentally by Tatum, Waters and co-workers and clinically by Lundy and Tovell (1934) at the Mayo Clinic.

SYNTHESIS—Diethyl malonate is treated with ethyl bromide in the presence of sodium ethoxide, and converted to diethyl malonate This is then alkylated with 2 bromo-pentane which results in 1,3 diethyl methyl butyl ethyl malonate This is then condensed with thiourea in the presence of sodium ethoxide which results in 5 ethyl 5 methyl butyl thiobarbituric acid The pure acid is precipitated from an aqueous solution of the reaction mixture by the addition of an acid

PROPERTIES—Thiopental is a pale yellow hydroscopic powder with a bitter taste which is readily soluble in water and partly soluble in alcohol insoluble in ether and benzine. Oil/water partition coefficient is 4 7 (0.214 pentobarbital) Six parts of sodium carbonate are added per 100 parts to prevent precipitation of insoluble free acid by atmospheric carbon dioxide and to serve as a buffer

Aqueous solutions are strongly alkaline pH of 2½% solution equals 10.5–12.

STABILITY—Atmospheric carbon dioxide precipitates the free acid from aqueous solutions. Solution not boilable or stable on standing. Packed in sealed ampules to prevent deterioration. Powder stable for several years. 5% solution deteriorates on standing at room temperature Unclear solutions not fit for clinical use. At 20°C particles appear in solution on third day At 5° cloudiness delayed until the eighth day

Not compatible with acidic substances. Compatible with blood, saline and dextrose solutions.

Cortex—Acts primarily at this site Depresses from above downward. Amount of depression varies with dose and rapidity of administration. Additional fractions depress subcortical areas and brain stem. Easily penetrates blood brain barrier Onset of hypnosis abrupt within 30–40 seconds. Recovery rapid after small dose with some somnolence and retrograde amnesia Not an analgesic Presumably does not block lemnisco-thalamic system. Blocks reticular activating system Must be combined with narcotic or anesthetic (N_2O) to block reflex activity Inhibits convulsions, particularly those of cortical origin. Less effective for those of spinal or other origin.

Brain—No localization of barbiturate in any subdivision of the brain. A lag in uptake by the brain. Peak is attained by thiobarbiturate in 7 minutes Brain exerts less destructive action than other tissues and retains drug longer Possibly due to binding by protein. 5% or more thiopental bound to protein of brain.

Intracranial Pressure—Unchanged ordinarily May be decreased if hypotension develops. May increase in hypoventilation. Concentration of drug in plasma and spinal fluid parallel each other May cause apnea if administered when pressure is increased. Spinal fluid varies with amount of CO_2 retained.

Electroencephalogram—Five definitely reproducible levels are recognized.

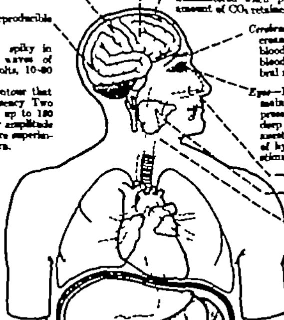
Level I—High amplitude fast waves, spiky in appearance Intraspersed with fast waves of slightly less amplitude—75–80 microvolts, 10–20 cycles per sec

Level II—Slow wave forms irregular contour that turn at random Wide variation in frequency Two cycles per sec or more in amplitudes up to 180 microvolts "Spiky waves of irregular amplitude with frequencies of 10 cycles per sec are superimposed on and between slow wave pattern.

Level III—Suppression appears Diphasic bursts within intervening quiet period Suppression less than 3 sec duration First phase has frequency of 10 cycles per sec Second phase 2 or more slow waves, 2 cycles per sec merging into the next suppression

Level IV—Suppression phases lasting 3–10 sec appear Activity as in Level III with less amplitude.

Level V—Amplitude decreased to less than 25 microvolts and single waves appear at 10 or more sec intervals.



Cerebral Blood Flow—Blood flow increased due to increased tone of cerebral vessels, due to increased blood CO_2 from respiratory depression. Cerebral blood flow varies with amount of CO_2 retained. Cerebral metabolism reduced.

Eyes—Pupils react to light during light hypnosis. Remain contracted. Nystagmus or divergent strabismus present. Eyeballs fixed. Pupils in mid-dilatation in deep hypnosis. Pupils become normal in size in light anesthesia. Eye signs not satisfactory index of depth of hypnosis. Corneal reflex remains active. Corneal stimulation during eye surgery elicits sneezing.

Cilia—Activity reduced.

Salivary Glands—No production or secretion of mucous. No irritation to the mucous membranes. Secretions cease to form during narcosis.

Thyroid—No effect. Patients with hypothyroidism manifest intolerance. Hyperthyroids may manifest increased tolerance.

Temperature Regulating Center—Depressed. Body temperature falls. Hypothermia develops when placed in cold environment. Shivering occurs on recovery if exposed to a cold environment. Body temperature falls.

Pharynx—Pharyngeal or gag reflex not abolished. May be accentuated. Local stimulation by airways, laryngoscopes, secretions may elicit cough, retching or severe laryngeal and bronchial spasm. Topical anesthesia blocks afferent impulses and prevents spasm.

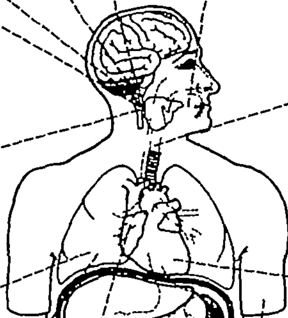
Respiratory Center—Depressed. Becomes progressively less sensitive to carbon dioxide

Vagus Center—Remains active

Vasomotor Center—Depressed during induction and during narcosis. Blood pressure may fall during induction but returns to normal during maintenance. May be depressed before respiratory center

Larynx—Laryngeal reflex not abolished. May be accentuated and be hyperactive. Severe laryngeal spasm may develop after instrumentation or stimulation by instruments, blood, mucous, or other stimuli. Topical anesthesia blocks afferent impulses and prevents spasm. Atropine not prophylactic except to abolish secretions which may stimulate. Severe spasm overcome by neuromuscular (striated muscle) blocking agents.

Spasm frequent when used as induction agent for "irritating" anesthetics, such as ether



Vomiting Center—No stimulating effect on center proper or chemoreceptor zone. May depress center and inhibit vomiting. Post-anesthetic vomiting due to drug itself uncommon. Post surgical vomiting due t factors other than anesthesia occur

Heart—Direct myocardial depressant. Degree of depression proportional to the amount of drug in contact with the heart. Repeated injections have cumulative effect on the heart. Unhealthy myocardium more susceptible to drug than healthy.

Arrhythmias may appear due to retention of CO_2. Uncommon with adequate ventilation. P.R. interval may be shortened. Does not sensitize the heart to epinephrine or other sympathomimetic amines. Rapid administration may cause severe myocardial depression and cardiac arrest. Rate variable, usually increased to compensate for vascular dilatation and other vascular changes.

Carotid, Aortic Chemoreceptors—Depressed by large doses. Remains active ordinarily nd reflexly maintains respiration when respiratory center insensitive to carbon dioxide and hypoventilation causes anoxia. Administration of oxygen causes apnea by removal of chemoreceptor drive.

Lungs—Potent respiratory depressant. Rhythm may be irregular. Rate and depth of breathing are decreased. Minute volume exchange reduced. Apnea common after initial injection. Total blood CO_2 increased. Carbon dioxide tension increased (alveolar)

Bronchi—Bronchi constricted. Bronchial spasm easily initiated by endoscopic instruments, secretions or foreign bodies. More common in asthmatics and bronchial-pulmonary diseases. Bronchospasm activity due to selective increase in reflex by thiobarbiturates. Prevented by blockade of impulses with topical anesthesia. Atropine decreases reflex activity and secretions which act as stimulus.

Blood Pressure—Effects vary with the rate of injection, state of the heart, peripheral circulation and quantity used. Rapid, intravenous injection causes abrupt fall in blood pressure accompanied by apnea. Slow injection may cause elevation at onset with widening of pulse pressure due to CO_2 retention (vasodilatation) and depression of vasomotor center. Reduction in pressure in hypertensives.

Metabolism—Reduced during hypnosis oxygen consumption decreased. Detoxified slowly when metabolism is decreased causing prolonged hypnosis.

Diaphragm—Hiccough may occur from manipulations of upper abdomen or when phrenic nerve is stimulated during operation.

Liver—Function not significantly altered. Liver glycogen depleted after large doses. Icterus index not changed. Hepatic dysfunction prolongs hypnotic effect. Bulk of drug detoxified here.

Adrenal—Adrenalectomy prolongs time required for detoxification.

Kidney—No evidence of damage t normal kidney. Less than 0.3% excreted unchanged in urine. Urinary output not markedly ffected by ordinary anesthetic doses. Toxic doses cause temporary anuria. Renal vasoconstriction in deep hypnosis reduces renal blood flow and glomerular filtration. Causes oliguria.

Sphincters—Not relaxed ordinarily. Attempts at dilatation may initiate severe laryngeal spasm or bronchial spasm.

Spinal Cord—N effect on cord reflexes. Reflex responses to stimuli not abolished.

Produces spinal block if injected intrathecally. Highly irritating to nerve tissues. Causes irreversible changes in cord.

Bone Marrow—No suppression of activity. M y be injected into medullary cavity in absence of veins.

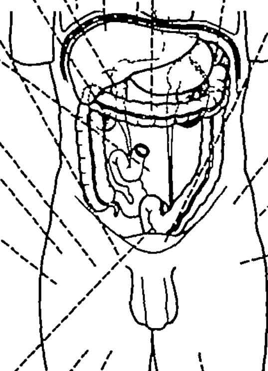
Nerves—Produces blockade when applied perineurally. Irritating to perineural tissues.

Reflexes—Deep reflexes depressed in deep basal narcosis. Remain active in ordinary hypnotic doses. Superficial reflexes may be present in light hypnosis but depressed in deep hypnosis. Painful stimuli cause movement due to failure to block pathways from periphery t the cortex. Movements due to lack of analgesic activity. Anesthesia develops with loss of all reflexes in massive doses, presumably due t block of bulbo-thalamic system.

Rectal—Absorbed by the rectum. Produces basal narcosis not adequate for surgical anesthesia. Doses used 1 gram per 30 lbs. body eight. Usually administered as 10% solution, 0.4 cc per lb of body weight. Maximum dosage should not exceed 3 grams.

Local Irritation—Highly irritant to subcutaneous tissues ad itions of arteries due to high alkalinity. Necrosis or fibrosis occurs in tissues if extravasation occurs. Inadvertent injection into radial artery causes severe spasm which may be followed by gangrene. More frequent with more concentrated solutions. Treatment. Use vasodilating block and anticoagulant. Venous thrombosis occurs in small percentage of cases.

Effect of Muscle Relaxants—No alteration on plasma levels, plasma time curve, electroencephalogram or sleeping time.



Autonomic Nervous System—Effects variable. No apparent change may be present in some cases. Generally parasympathetic effects appear to predominate. Heart more responsive to vagal impulses. Bronchial constrictor tone increased.

Gastro-intestinal System—Effects variable. Smooth muscle depressed by large doses. Light hypnosis causes general increase in tonus. Drug destroyed on passage through gastro-intestinal tract. Thiobarbiturates ineffective if administered orally except in large doses.

Spleen—Usually constricted if blood pressure rises or hypoventilation is present. May dilate.

Uterus—Frequency and amplitude of contractions remain unchanged in light hypnosis, reduced in deep hypnosis. Drug passes through placental membrane to the fetus and causes respiratory distress at birth. Fetal arterial blood content equals maternal blood content after 15 minutes.

Muscles—Ordinarily muscle relaxation inadequate for surgery. Necessitates use of muscle relaxants. Relaxed in deep hypnosis and in toxic doses. External stimuli during light hypnosis increases muscle tone. Exerts little or no curariform effect. Causes irritation when injected into muscle but not as pronounced as subcutaneously.

Skin—Temperature rises several degrees due to peripheral vasodilatation. Sweating absent. Skin remains dry and pink. Skin rashes due to allergy possible but rare.

Tissue Concentrations—Plasma concentration falls rapidly for the first 15 to 30 minutes after single intravenous injection. Maximum tissue concentration reached one minute after injection, thereafter declines t a rate parallel to plasma level in all tissues except muscle and fat. Muscle concentration attains equilibrium within 15 minutes after injection. Initial short action due to diffusion from brain to blood and to rapid uptake by tissues. Equilibrium attained by plasma brain and body tissues as successive doses are added. Rate of destruction slow—10–15% per hour.

Stored in adipose tissues. Perirenal omental nd lumbar fat contain 3 to 25 times plasma level. Muscle only 1–3 times. Lipoids contain 30 times as much as muscle. Peak level in adipose tissue occurs within 2 hours, not complete until 4 hours later.

Metabolized completely in man. 25% oxidized to carboxylic acid. Less than 5% desulphurated. Cumulative effect observed if dose is repeated within 30 hours. Carboxyl group is on terminal carbon of methyl butyl side chain.

Tolerance—Acute tolerance develops to rapid injection. Chronic tolerance to repeated injection. Second injection after several days produces less effect than first. Cross tolerance also seen with other barbiturates.

Oxygen Capacity—Usually unchanged if ventilation is adequate.

Oxygen Content—Venous and arterial content not significantly changed.

Blood Sugar—Variable, slightly increased or unchanged in both normal and diabetic patients.

Clotting Time—Unchanged.

Bleeding Time—Unchanged

Non-protein Nitrogen—No significant changes.

Red Blood Cells—No significant hemolysis due to intravenous injection. No hematuria. No intravascular hemolysis. No changes in morphology

Blood Concentration—Plasma level falls rapidly after injection. Acidosis suppresses blood level. Concentration of drug at which the patient awakens increases as duration proceeds. Patient awakes at higher plasma level when large initial dose has been used than after small dose. Acute tolerance develops to narcotic effect. Equilibrium develops between tissues, brain and plasma after successive fractional administration.

Blood Volume—Usually no change. Slight hemodilution may occur. Hemoconcentration may occur with hypoventilation.

Plasma Volume—Usually no change. May increase slightly

Red Blood Cells—Usually no change. Usually increased in number with hemoconcentration and decreased if hemodilution is present.

Carbon Dioxide Content—Increased due to depression of respiration. Causes respiratory acidosis. Increase proportional to depression.

Carbon Dioxide Combining Power—No significant changes in light hypnosis. May decrease in deep hypnosis.

Blood pH—Usually slightly decreased due to respiratory acidosis. Decrease of pH suppresses plasma level due to the formation of the free acid which passes into the fat. Decrease of pH from 7.35 to 6.8 (with CO_2) reduces plasma level 40%.

Blood Proteins—No significant change. Barbiturate bound to protein—mostly albumin. Degree of binding varies with pH. Binding is reversible and dependent upon albumin concentration. As much as 60–70% thiopental adsorbed to protein. Binding maximal at pH 8. Bound compound does not play role in hypnosis.

USES

1. As an anesthetic for brief surgical procedures.
2. As a basal hypnotic to supplement nitrous oxide, ethylene and other anesthetics of low potency or in combination with analgesics.
3. To relieve convulsive states produced by stimulating drugs or other causes.
4. As hypnotic in conjunction with regional anesthesia (spinal, nerve block, etc.).
5. For narco-analysis in psychiatric disorders and narco-interrogation in criminal investigation.

MODE OF ADMINISTRATION

Intravenous. In fractions using 2½% solution. Total dose not to exceed one gram. Not suitable as a sole agent. Should always be employed with an agent with analgesic properties to abolish reflex activity and minimize total quantity used. Test dose of 50 mgm. to detect intolerance advised.

ADVANTAGES

1. Induction simple, rapid, pleasant.
2. Requires a minimum of apparatus.
3. Non-irritating to the respiratory tract
4. Does not cause formation of secretions.
5. Allows the use of cautery and other devices which may be source of ignition.
6. Recovery rapid without nausea and vomiting after minimal doses.

DISADVANTAGES

1. Not analgesic. Requires use of nitrous oxide, vinyl ether, trichlorethylene, meperidine or other analgesic agents.
2. Causes severe respiratory depression.
3. Non-controllable as a sole anesthetic.
4. Cumulative action invariably occurs if one gram doses are exceeded.
5. Muscle relaxation not adequate (use relaxant)
6. Superficial reflexes not abolished. Painful stimuli cause movement.
7. Solutions irritating—may produce slough, thrombosis or arterial spasm.
8. Variations in susceptibility between patients.
9. May be myocardial depressant.
10. Prolonged somnolence may develop in intolerant individuals or those with depressed metabolism.

PATHOLOGY

No pathologic effects directly ascribable to the drug noted in acute toxicity. No specific lesions in chronic toxicity. Neurologic changes in brain may follow acute poisoning with massive overdoses in recovery period, probably due to anoxia.

CONTRAINDICATIONS

1. Ambulatory patients.
2. Inadequate airway before induction—obesity, Ludwig Angina, compression of trachea, etc.
3. Porphyria.
4. Respiratory distress—status asthmaticus, dyspnea, orthopnea, etc.
5. Acidosis from any cause, renal, diabetic or other
6. Addison Disease.
7. Cardiac decompensation.
8. Shock.
9. Situations which may prolong narcotic effect, over-premedication, hepatic dysfunction, acidosis, etc.
10. Situations in which airway cannot be maintained after induction.
11. Severe anemias, hypovolemia.
12. Elevated intracranial pressure.
13. Severe hypothyroidism.
14. Dystrophia myotonica.

USE UNDESIRABLE

1. Children.
2. Myasthenia gravis.
3. Obstetrics
4. Myocardial disease with poor reserve.
5. Borderline reduced pulmonary reserve.

ULTRA SHORT ACTING THIOBARBITURATES

Name	Thiamylal	Methitural	Thialbarbitone	Buthalitone
Synonym	Surital	Neraval, Thiogenal	Kemithal	Transithal, Baytinal
History	Developed by Parke, Davis Laboratory	Introduced by Dietmann 1954.	Carrington (England 1946)	Used clinically by Weese & Koss 1954.
Chemical Name	5 allyl 5' methyl butyl thiobarbiturate sodium.	5 butyl 5' methyl thioethyl barbiturate sodium.	5 allyl 5 cyclohexenyl thiobarbiturate sodium.	5 allyl 5 isobutyl thiobarbiturate sodium.
Oxygen analogue	Secobarbital	None	None	None
Color	Pale yellow powder	Pale yellow powder	Pale yellow powder	Pale yellow powder
pH of Na salt solution	Unstable solution 10.5–11	Unstable solution 10.5–11	Unstable solution 10.5–11	Unstable solution 10.5–11
Potency	Similar to thiopental.	Half of thiopental.	Similar to thiopental.	Similar to thiopental.
Administration	Similar to thiopental. 2% I.V.	As 5 or 8% solution.	As 5–10% I.V.	As 10% solution I.V.
Maximum Dose	Slightly less than thiopental.	Greater than thiopental. Not to exceed 6 gm.	Half as potent as thiopental.	1–1.5 grams.
Anesthetic Dose	Slightly less than thiopental.	Greater than thiopental.	Equipotent doses produce same effect.	0.5–0.8 gram.
Smoothness of induction	Similar to thiopental.	Rapid but not smooth.	Rapid but not smooth.	Rapid but not smooth.
Recovery	More rapid than thiopental.	More rapid than thiopental (½ times)	More rapid than thiopental.	More rapid than thiopental (½ times)
Hangover effects	Present. Similar to thiopental.	Present. Less than thiopental.	Present. Less than thiopental.	Present. Less than thiopental.
Local Irritation	Same as thiopental. Causes slough, thrombosis, arterial spasm.	Same as thiopental. Causes slough, thrombosis, arterial spasm.	Same as thiopental. Causes slough, thrombosis, arterial spasm.	Same as thiopental. Causes slough, thrombosis, arterial spasm.
Reflexes	Similar to thiopental. Painful stimuli cause movement.	Similar to thiopental. Painful stimuli cause movement.	Similar to thiopental. Painful stimuli cause movement.	Similar to thiopental. Painful stimuli cause movement.
Cerebral metabolism	Similar to thiopental.	Similar to thiopental.	Similar to thiopental.	Similar to thiopental.
Cerebral blood flow	Similar to thiopental	Similar to thiopental	Similar to thiopental	Similar to thiopental
Electroencephalographic changes	Same as thiopental.	Same as thiopental.	Same as thiopental.	Same as thiopental.
Convulsive effects	Twitchings absent. Inhibits convulsions same as thiopental	Twitchings absent. Inhibits convulsions same as thiopental.	Twitchings absent. Inhibits convulsions same as thiopental.	Twitchings absent. Inhibits convulsions same as thiopental.
Myocardial effects	Qualitatively similar to thiopental.	Qualitatively similar to thiopental.	Qualitatively similar to thiopental.	Qualitatively similar to thiopental.
Cardiac Rhythm	Arrhythmias absent.	Arrhythmias absent.	Arrhythmias present.	Arrhythmias absent.
Pulse Rate	Increase in pulse rate.	Slight increase, less than thiopental.	Slight increase in pulse rate.	Slight increase in pulse rate.
Blood Pressure	Post-injectional depression	Post-injection decrease 10–40% for several minutes with partial recovery	Decrease post-injection 10–40% with partial recovery	Post injection decrease with partial recovery
Respiration	Depresses. Qualitatively similar to thiopental	Depresses. Qualitatively similar to thiopental.	Depresses. Qualitatively similar to thiopental.	Depresses. Qualitatively similar to thiopental.
Laryngeal and bronchial reflexes	Spasmogenic, similar to thiopental	Greater frequency than thiopental.	Similar to thiopental.	Spasmogenic, coughing, sneezing, hiccough.
Body temperature	Depresses center similar to thiopental	Depresses center similar to thiopental.	Depresses center similar to thiopental.	Depresses center similar to thiopental.
Blood brain barrier	Easily penetrates. Rapid onset. Equal to thiopental in uptake.	Easily penetrates. Rapid onset. Equal to thiopental.	Easily penetrates. Rapid onset. Equal to thiopental.	Easily penetrates. Rapid onset.
Uptake by adipose tissues	1½ times greater than thiopental. Accounts for rapid recovery	Rapid, equal to thiopental. Accounts for rapid recovery.	Similar to thiopental but 45% less. Accounts for rapid recovery	Similar to thiopental. Accounts for rapid recovery
Effects on smooth muscle	Depresses in deep hypnosis	Depresses in deep hypnosis.	Depresses in deep hypnosis.	Depresses in deep hypnosis.
Effects on uterus	Passes placental barrier. Depresses fetal respiration	Passes placental barrier. Depresses fetal respiration	Passes placental barrier. Depresses fetal respiration.	Passes placental barrier. Depresses fetal respiration.
Detoxication	In liver similar to thiopental.	In liver about 50% per hour	Metabolized by liver. 0.5% eliminated unchanged.	In liver similar to thiopental.
Effects with muscle relaxants	Qualitatively similar to thiopental	Qualitatively similar to thiopental.	Qualitatively similar to thiopental.	Qualitatively similar to thiopental.
Muscle relaxation	Not adequate. Relaxant required.	Not adequate. Relaxant required.	Not adequate. Relaxant required.	Not adequate. Relaxant required.

N-SUBSTITUTED BARBITURATES AND SHORT ACTING BASAL NARCOTICS

Name	Hexobarbital	Methohexital	Dolitrone	Glutethimide
Synonym	Evipan, evipal, hexobarbitone	Brevital	M.R.D. [illegible]	Doriden
History	Weese (Germany) 1932	Developed by Gruber [illegible]	Introduced by Lundy [illegible]	Prepared by Tagmann, et al. [illegible]
Chemical Name	5 methyl 5 cyclohexenyl N methyl barbiturate sodium.	5 allyl 5 1 methyl 2 pentynyl N-methyl barbituric acid.	5 ethyl 6 phenyl metathiazane 2,4 dione sodium	Alpha ethyl phenyl glutarimide
Oxygen analogue	None	None	None	None
Color	White, stable	White, stable.	White lyophilized power	White
pH of N salt solution	Unstable 10 [illegible]	Unstable 10–11	Acid insoluble Na salt soluble 11.[illegible] [illegible] crystallizes out on standing.	Insoluble in water. Soluble in organic solvents.
Potency	Non-analgesic, compares with thiopental	Non-analgesic, more potent than thiopental	Non-analgesic, less potent than thiopental.	Non-analgesic, less potent than thiopental
Administration	10% solution I.V. rectal.	1.0% solution by drip technique	Intravenously as [illegible]% solution.	Only satisfactory orally as tablet for hypnosis. I.V. in propylene glycol
Maximum Dose	1 gram	[illegible] gm.	1 gram	[illegible] gm. orally
Anesthetic Dose	0.1–[illegible] gm.	[illegible] mgm. I.V.	[illegible] gm.	About ½ as potent as secobarbital
Smoothness of induction	Not as smooth as thiopental.	Smooth without excitement.	Rapid onset, smooth.	Not satisfactory intravenously
Recovery	More rapid than thiopental.	More rapid than thiopental.	Rapid with excitement.	Once deep hypnosis is obtained it is sustained for hours.
Hangover effects	Present, for several hours afterward	Present, for several hours afterward.	Present, but not as intense as with thiopental.	Present.
Local Irritation	Less than with thiopental.	Less than with thiopental.	Marked local irritation.	Parenteral solution causes phlebitis.
Reflexes	Not abolished. Painful stimuli cause movement. Not analgesic	Not abolished. Painful stimuli cause movement. Not analgesic.	Not abolished. Painful stimuli cause movement. Not analgesic.	Massive doses depress. Not analgesic.
Cerebral metabolism	Depressed.	Probably depressed.		Depressed.
Cerebral blood flow	Decreased			
Electroencephalographic changes	Decreased activity similar to thiopental	Slowing in frequencies—[illegible] cycles per sec.	Decreased activity	Same as secobarbital.
Convulsive effects	Twitchings and neuromuscular activity present.	Present but much less than with thiopental	Absent. Antagonizes convulsions.	Absent.
Myocardial effects	Similar to thiopental.	Similar to thiopental	Depresses, qualitatively similar to thiopental.	Sedative doses no effect.
Cardiac rhythm	No irregularities	Absent	Absent.	No effect in sedative doses.
Pulse Rate	Increased.	Increased.	Increased	Not altered in sedative doses.
Blood Pressure	Post injection depression.	Post-injection depression.	Post injection depression.	Slight hypotension I.V.
Respiration	Depressed, less than thiopental	Depresses, similar to thiopental	Depressed, less than thiopental.	No effect in hypnotic doses
Laryngeal and bronchial reflexes	Active, less spasm than thiopental.	Active, less spasm than thiopental.	Active, laryngeal and bronchial reflexes obtunded	Active. Large doses obtunded.
Body Temperature	Decreased.	Depressed.	Depressed.	Depressed in overdosage
Blood Brain Barrier	Rapid penetration, equal to thiopental.	Rapid penetration, equal to thiopental	Rapid penetration, equal to thiopental.	
Uptake by Adipose Tissue	Uptake approx. [illegible] that of thiopental	Less than thiopental	Equal to thiopental.	Taken up by lipoids.
Effects on Smooth Muscle	Depresses.	Depresses	Depresses.	No appreciable effect in hypnotic doses.
Effects on Uterus	Similar to pentothal. Passes into fetal circulation	Similar to thiopental. Passes into fetal circulation.	Passes placental barrier	Passes placental barrier
Detoxification	Detoxified by desmethylation in liver	Rapidly detoxified by liver		Excreted in bile and re-absorbed
Effects with Muscle Relaxants	Similar to thiopental.	Compatible. Similar to thiopental	Similar to thiopental.	Not used
Muscle Relaxation	Poor. Fasciculations present throughout.	Poor. Fasciculations and other signs of neuromuscular activity	Poor. Tremors and fasciculations absent	Poor. Tremors and fasciculations absent.

URETHANES (CARBAMATES) AND SUBSTITUTED UREAS

	Urethane	Hedonal	Aponal	Carbromal	Bromural	Sedormid
History		Used as an intravenous anesthetic by Page in 1912.		Introduced by Bayer. Also known as uradal, adalin.	Bromvaleryl.	Developed by Roche Laboratory
Chemistry	Ethyl ester of carbamic acid. Colorless, odorless crystals—very soluble in water alcohol.	Carbamic acid ester of methyl propyl carbinol. White powder melts at 74 to 76° Soluble in water and organic solvents.	Tertiary amyl carbamate. White crystalline powder with a camphorlike odor Soluble in water and organic solvents.	White crystalline odorless powder Slightly soluble in water Soluble in organic solvents. Melts at 116 to 117°C.	Monobrom iso valeryl urea. White tasteless powder Melts 147 t 149° Soluble in cold water and organic solvents.	Allyl isopropyl acetylcarbamide White t t l as powd r melting at 194 Insoluble in cold water Similar to carbromal. Soluble in hot and organic solvents.
Potency	Mildly hypnotic More potent in animals than man Rapidly absorbed from the G.I. tract Not analgesic. Hypnosis lasts four or five hours.	Twice as potent as ethyl urethane Esters of secondary alcohols are more potent than primary Not analgesic.	Somewhat more potent than hedonal. Esters of tertiary alcohol are more potent than secondary Not analgesic.	Feebly hypnotic with potency similar to bromides Not analgesic.	Similar to carbromal in potency Possesses no analgesic properties.	Similar to carbromal.
Toxicity	May arrest cell mitosis. Depresses bone marrow Excreted as urea after hydrolysis. Probably by detoxified liver	More toxic than urethane. Absorbed more slowly Believed t be excreted as urea and amyl alcohol after hydrolysis.	Similar to hedonal. Excreted as urea and amyl alcohol.	Eliminated partly unchanged in urine and partly in form of inorganic bromides.	Similar t carbromal.	Similar to other substituted amides. Causes depression of platelet production, resulting in thrombocytopenic purpura.
Systemic effects	Hypnosis and narcosis accompanied by little or no changes in respiratory and circulatory systems	Similar to ethyl carbamate	Similar t hedonal.	No remarkable effects on the circulatory or respiratory systems.	Similar t carbromal.	Same as carbromal.
Doses	Included in U.S.P Oral 1 t 4 gm.	Dose 1 to 2 gm orally	Dose ½ to 1 gm. orally	Dose 0.6 t 1.3 gm. orally	Dose 0.5 to 1.0 gm. orally	Dose 0.25 to 0.5 gm. orally Effect lasts five or six hours.
Uses	(1) As anesthetic for laboratory animals (2) To increase solubility of drugs such as quinine (3) T depress bone marrow in leukemia. (4) As a hypnotic. Has largely been superseded by barbiturates for human use	Used as hypnotic and sedative Use as an intravenous anesthetic is obsolete Has largely been superseded by barbiturates as a hypnotic for human use	As sedative and hypnotic. Has largely been superseded by barbiturates.	As a mild hypnotic or sedative Largely superseded by barbiturates for human use	As a mild hypnotic and sedative Little used today in man.	As a sedative and hypnotic. Possesses no analgesic properties.

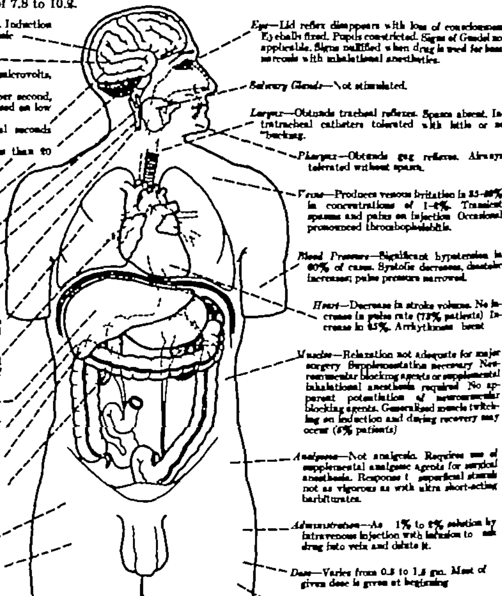
HYDROXYDIONE (VIADRIL)

HISTORY—Selye (1941) noted that certain steroids (related to the female sex hormones) produced cerebral depression. Since then others have observed similar responses with large doses of sterols. Lauback and associates at the Pfizer Laboratories developed 21-hydroxy pregnane 3,20-dione sodium succinate known as Viadril The compound is one of many which depresses the nervous system. It is one of the less toxic and has fewer side actions than others which have been studied.

First used clinically by F J Murphy and associates 1956 Investigated by many other clinicians also.

CHEMISTRY—The compound is the sodium salt of 21-hydroxy pregnane 3,20-dione hemisuccinate.

PROPERTIES—Viadril is a non-volatile water soluble white crystalline powder prepared as a sodium succinate ester Aqueous solutions have a pH of 7.8 to 10.2.



ADVANTAGES

(1) Non-spasmogenic to bronchi and trachea.
(2) Greater obtundation of superficial reflexes than occurs with thiopental.

DISADVANTAGES

(1) Phlebitis and pain on injection.
(2) Long latent period.
(3) Estimated dose must be given in toto for induction. Not as satisfactory if fractionated.
(4) Hypotension may develop.
(5) Not analgesic. Requires supplemental anesthetics and muscle relaxants.

USES

(1) As a basal narcotic in conjunction with nitrous oxide, cyclopropane or non-volatile (narcotic) analgesics.
(2) For endoscopic procedures when bronchial and laryngeal spasm are possibilities.

ATARACTICS (TRANQUILIZERS)

SYNONYM—Psychotherapeutic drugs. Also known as normalizers, calmatives, neurosedatives, psychic energizers. Terms are psychological, not pharmacological. The effect, therefore is produced by a varied group of drugs and not by specific drugs acting at specific sites

Ordinarily tranquility is accomplished by the use of central nervous system depressants. In certain depressed states, central nervous system stimulants are used

I Depressant drugs used are divided into

A Non-selective depressants (analgesics, anesthetics, narcotics and hypnotics)

B Selective depressants. These include

(1) anti-convulsants.
(2) anti-histaminics.
(3) muscle relaxants—mephenesin and allied spinal cord depressants.
(4) central parasympathetic depressants—benactyzine suavitil.
(5) central sympathetic depressants which act on subcortical areas—phenothiazines and allied drugs.
(6) sympathetic suppressants—Rauwolfia derivatives.

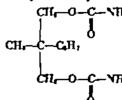
II Central stimulants. These include drugs acting on the cortex and subcortical areas—methylphenidate (Ritalin) pipradrol (Meretran)

THE CHEMICAL NATURE OF PSYCHOTHERAPEUTIC AGENTS

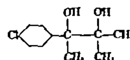
A. Phenothiazine Derivatives

1. Chlorpromazine is prototype of family of more than a dozen.

B Glycol and Glycerol Derivatives



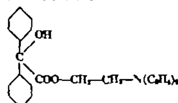
Meprobamate,



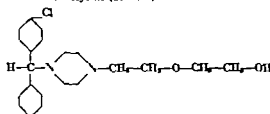
Phenaglycodol (Ultran)

C. Rauwolfia Alkaloids—Reserpine (Serpasil)

D Diphenylmethane Derivatives



Benactyzine (Suavitil)



Hydroxyzine (Atarax)

SIMILARITIES AND DIFFERENCES OF OTHER PHENOTHIAZINES TO CHLORPROMAZINE

Substitutions on side chain of phenthiazine result in series of chlorpromazine-like compounds similar in pharmacologic properties but varying in potency and toxicity

S
N

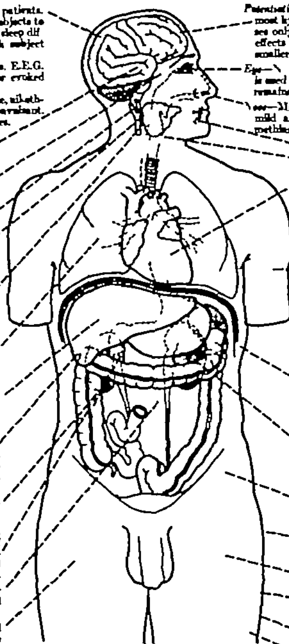
Name	Structure (substituent; side chain on N)	Chemical	Pharmacology	Toxicity Potency
Promethazine (Phenergan)	H; $-CH_2-CH(CH_3)-N(CH_3)_2$	Has diamino isopropyl group in position N	Central depressant. Potent anti-histaminic. Anti-emetic. A mild tranquilizer	Not as potent as adrenolytic agent. Not as potent as tranquilizer Dose 25–50 mgm.
Promazine (Sparine)	H; $-CH_2-CH_2-CH_2-N(CH_3)_2$	Same as chlorpromazine except it is minus the Cl.	Possesses some tranquilizing sympatholytic effect. Potentiating action as chlorpromazine.	Causes jaundice, hypotension, symptoms of Parkinsonism and similar other side effects as chlorpromazine. Dose 25–50 mgm.
Triflupromazine (Vesprin)	CF; $-CH_2-CH_2-CH_2-N(CH_3)_2$	Has CF_3 in place of Cl in chlorpromazine.	2–3 times more potent than chlorpromazine. More potent anti-emetic.	Less sedation, agitation, motor and hepatic effects. Dose 5–10 mgm.
Mepazine (Pacatal)	H; $-CH_2-$(piperidyl ring)$N-CH_3$	Has an N-methyl 3, piperidyl methyl group and no chlorine.	Anti-emetic tranquilizing, potentiator of narcotic. Mild anti-histaminic.	Less hypotensive effect than chlorpromazine. Less effect on liver. Suppresses bone marrow. Dose 25–50 mgm.
Prochlorperazine (Compazine)	Cl; $-CH_2-CH_2-CH_2N$(piperazine ring)$N-CH_3$	*Has N-substituted piperazine ring instead of diethyl amino group*	*Anti-emetic equal to* chlorpromazine. Tranquilizer similar to chlorpromazine.	*Drowsiness.* Some hypotension. Less hepatic and bone marrow effects. Dose 5–10 mgm.
Trifluoperazine (Stelazine)	CF; $-CH_2-CH_2-CH_2-N$(piperazine ring)$N-CH$	Has CF in place of Cl in prochlorperazine.	Ten times more potent. One-tenth as active in potentiating barbiturates.	Similar to chlorpromazine. Fewer side actions. Dose 5 mgm.
Thiopropazate (Dartal)	Cl; $-CH_2-CH_2-CH_2-N$(piperazine ring)$N-CH_2-CH_2-O-C(=O)-CH_3$	Has N-substituted piperazine group instead of diethyl amino group	More potent than chlorpromazine.	Toxic manifestations not increased in proportion to potency Dose 5–10 mgm.
Perphenazine (Trilafon)	$-CH_2-CH_2-CH_2-N$(piperazine ring)$N-CH_2-H_2-OH$	Has N-substituted piperazine ring instead of amino group.	More potent than chlorpromazine	Toxic manifestations less than chlorpromazine. Dose 4–8 mgm.

CHLORPROMAZINE (THORAZINE)

HISTORY—Phenothiazine derivatives first synthesized by Bernthsen (1883). French investigators noted sedative effects in 1945. Laborit (France) promethazine (Phenergan) to supplement nitrous oxide anesthesia. Charpentier synthesized chlorpromazine 1950.

SYNONYMS—Thorazine. Largactil.

CHEMISTRY—Chlorpromazine is 2, chloro, 10 (dimethylaminopropyl) phenothiazine. Forms a salt with hydrochloric acid which is a grayish white powder soluble in water acid in reaction (pH 5). Solution turns brown on exposure to light. Must be stored in light proof containers. Powder stable.



Cortex—Reduces motor activity of hyperactive patients. Single doses do not alter ability of normal subjects to perform psychologic tests. Produces state of sleep different from general anesthesia from which subject may be aroused.
No direct effect on cortex by single doses. E.E.G. not altered. Does not alter spontaneous or evoked burst discharge or cortical changes.
Antagonizes psychomotor effects of caffeine, nikethamide and other stimulants. Not an anti-convulsant. Does not abolish electrically induced seizures.

Basal Ganglia—Toxic responses produce a reversible Parkinson-like syndrome. Develops after prolonged, sustained high dosage. May cause severe changes.

Reticular Activating System—Causes depression of ascending reticular activating system, produces somnolence.

Diencephalon—Depresses seat of autonomic system.

Vomiting Center—Potent antiemetic. Acts centrally. Suppresses vomiting due to central acting chemical agents, such as apomorphine.

Heat Regulating Center—Depressed if combined with narcotics or hypnotics. Body temperature tends to approach that of environment.

Lungs—Large doses depress respiration. Reduces depression caused by hypnotics by potentiating effect which reduces dose of hypnotic or narcotic necessary.

Liver—Produces obstructive type jaundice. Appears to be dosage related. More common in higher dose than sustained administration.

Detoxification—None recovered in urine. 10% may appear as sulphoxide. Chlorpromazine, sulphoxide similar in pharmacologic properties as chlorpromazine but less active.

Kidney—No appreciable changes caused by drug.

Adrenal—Exerts an antiepinephrine and norepinephrine effect. Prevents release of A.C.T.H. and release of gonadotropic hormone. Endocrine functions also decreased due to direct suppression of diencephalon.

Spinal Cord—No appreciable effect on either monosynaptic or polysynaptic mediated reflexes.

Peripheral Nerve—Does not change potential evoked by single stimuli. Possesses some local anesthetic activity.

Potentiation of Sedatives—Increases sleeping time of most hypnotics. Enhances the effects of ether. Possesses only a slight analgesic activity but enhances the effects of true analgesics, permitting control with smaller doses.

Eye—No appreciable changes in single doses or if drug is used alone. *Lid reflex remains intact. Corneal reflex* remains intact.

Nose—May cause nasal stuffiness, dry mouth. Possesses mild antihistamine activity. Much less than promethazine.

Pharynx—No changes.

Larynx—No changes.

Heart—Tachycardia may follow large doses. No appreciable effect on myocardium. No electrocardiographic changes. Tends to suppress arrhythmias. Causes coronary vasodilatation. Antagonizes arrhythmias produced by epinephrine in conjunction with hydrocarbon anesthetics.

Blood Pressure—Abolishes pressor response to stimulation of the vagus.
Causes orthostatic hypotension. More common following parenteral use after the use of general anesthesia or surgery. Severe fatal peripheral circulatory failure may occur after intravenous administration.
Prevents pressor response to epinephrine and norepinephrine.

Body Temperature—Falls. Due to (a) sympatholytic action of drugs resulting in peripheral dilatation, (b) reduction in muscle activity, (c) cold external environment and (d) inactivation of heat regulating center.

Gastro-Intestinal—No significant effects. Large doses may cause gastric irritation and reduce gastric secretion. No appreciable effect on smooth muscle when used alone.

Muscle—Decreases response to both direct and indirect stimulation. Does not act at myoneural junction.

Skin—May cause eruptions due to contact dermatitis. May also cause photosensitization.

Bone Marrow—May produce agranulocytosis, aplastic anemia or pancytopenia.

Autonomic Nervous System—Produces a ganglionic depressant effect. Partly responsible for hypotension.

Arterioles—Causes relaxation of vascular bed due to sympatholytic effect.

Tissues—Leaves blood quickly. Highest concentration in brain. Lowest concentration in lungs, spleen, kidney, liver.

DOSAGE—After oral administration effects apparent in ½ hour, peak reached in one hour. Lasts several hours. Effective orally. Irritating subcutaneously. Intravenous dose may cause circulatory collapse. Dosage must be individualized. Varies from 10-50 mgm.

CONTRAINDICATIONS—1. Marked central nervous depression. 2. Liver disease. 3. Surgery or anesthesia in patients with cardiovascular disease, hypovolemia, anemia. 4. Hypothyroidism. 5. Adrenal insufficiency.

USES—1. As tranquilizer for mental diseases. 2. To potentiate narcotics, hypnotics, and anti-convulsants. 3. As an antiemetic. 4. To depress the heat regulating center.

OBJECTIONS—1. Causes difficult to reverse hypotension, particularly during operation and surgical anesthesia. 2. Suppresses [illegible]row activity. 3. May cause jaundice. 4. May cause F[illegible]

SEDATIVES AND HYPNOTICS

Name	Meprobamate	Hydroxyzine	Ethinamate	Ethchlorvynol	Methyprylon
Synonym	Miltown, Equanil	Atarax, Vistaril	Valmid	Placidyl	Noludar
Chemistry	dicarbamic acid ester of 2, methyl 2, n-propyl, 1,3 propanediol.	1(p-chlorobenzyl hydro-dryl-4 (2-2 hydroxy ethoxy ethyl piperazine.	1,ethynyl cyclohexyl carbamate	A halogenated triple bonded alcohol. Has triple and double bonded and saturated side chain on methanol. Beta chlor vinyl ethynyl, ethyl carbinol.	3,3 diethyl 5,methyl, 2,4 piperidinedione
Properties	Chemically allied to mephenesin. Stable white powder M.P 105°C. Poorly soluble in water	Forms a hydrochloride.	White powder	Stable.	Stable, white powder
Major actions	As a central muscle skeletal relaxant. Anti-convulsant. Antagonizes metrazol and strychnine convulsions.	Some tranquilizing effect similar to phenothiazines. Sedation.	Sedative and hypnotic.	Sedative and hypnotic. Non-analgesic.	Hypnotic and sedative Not an analgesic.
Sites of action	Depresses internuncial neurons in cord. No effect on monosynaptic neurons. Suppresses thalamus.	Some cortex, possibly mid-brain.	Non-specific. Act on cortex like barbiturates.	Non-analgesic. Acts on cortex. Produces additive effect with other hypnotics. Daytime sedative.	Cerebral cortex. Similar to barbiturates. Not much different in responses. Daytime sedative.
Side actions	Not antihistaminic. Possesses no autonomic effects. Does not act t myoneural junction.	Slightly anti-histaminic. No sympatholytic effect.	Non-analgesic.	Hangover effect noted. N effects on liver kidney or bone marrow	No effect on liver, kidney or bone marrow
Toxic effects	Large doses depress centrally Wide margin of safety	Toxicity low No hepatic effect Does not depress bone marrow	Respiratory depression in massive doses.	Overdosage results in respiratory failure.	Overdosage results in respiratory failure
Elimination	10% unchanged, 90% conjugated as glycuronate.		Completely metabolized probably by hydrolysis.	Undergoes detoxification in liver Bilateral nephrectomy does not enhance duration.	Dehydrogenated to tetrahydropyridine hich may be toxic to bone marrow
Dose	Used orally Intravenously causes thrombosis, hemolysis.	Used as daytime sedative for symptomatic management of neurosis.	500 mgm. orally as hypnotic.	500 mgm. Onset 20–30 minutes. Lasts 4–6 hours	50–100 mgm. orally for hypnosis.

SECTION X. OPIUM ALKALOIDS AND SYNTHETIC ANALGESICS

THE OPIUM ALKALOIDS

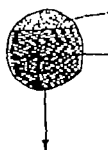
Opium is the dried resinous exudate derived by incising the unripe capsule of papaver somniferum (opium poppy). The plant is found in Asia Minor, China and certain Mediterranean areas.

SOLUTIONS

Tincture—10% solution in alcohol (1 cc. = 0.1 gm. opium = 10 mgm. morphine)

Camphorated tincture—1/25 (4 gm.) of amount of opium in the tincture plus camphor (4 gm.) benzoic acid (4 gm.) and oil of anise (4 cc.) per liter of 10% alcohol.

Pantopon—Solution of total alkaloids of opium in form of hydrochloride: 1/10th of weight of alkaloids is morphine



Opium Powder Contains

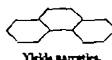
- *alkaloids*
- *pectin*
- *waxes*
- *sulphates*
- *lactates*
- *meconic acid*

Powder

U.S.P.: 10% consists of alkaloids by weight.

Yields approximately 25 alkaloids. Divided into two groups.

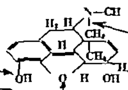
Phenanthrene Group



Yields narcotics.

Isoquinoline Group (Papaverine most important.)





Phenolic hydroxyl group determines narcotic potency

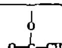
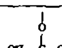
Ethereal oxygen is inert.

Tertiary N gives basic properties, forms salts with acids.

OH not phenolic due to partial hydrogenation of ring: responsible for convulsive effects.

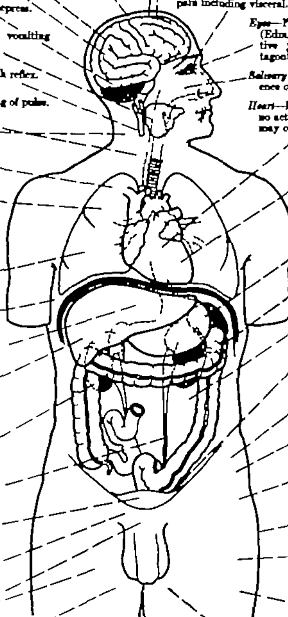
Alteration of either hydroxyl of morphine alters narcotic or convulsive effect.

Morphine (U.S.P.)
Intensity of action, duration of action, and analgesic effect most pronounced of whole group: habit-forming.

Methylation of phenolic hydroxyl decreases potency	 O—CH	Both hydroxyls methylated results in *thebain* (convulsant)	 OH	*Codeine* (U.S.P.) Least potent, dose required 4 to 6 times that of morphine: habit-forming.
Ethylation of phenolic hydroxyl decreases potency. Produces dionin	 O—C_2H_5		 OH	*Dionin* *Action equivalent to codeine*
Both hydroxyls acetylated: narcotic effect enhanced approximately six times.	 O—C(=O)—CH		 O—C(=O)—CH_3	*Heroin* Short, intense action; less side effects than with morphine: habit-forming.
Phenolic hydroxyl intact	 OH	Hydrogenation of double bond in ring 2, and conversion of hydroxyl to ketonic group.	 O	*Dilaudid* (N.N.R.) Less convulsant as analgesic as morphine 10 times more toxic than morphine: habit forming.
Phenolic hydroxyl methylated	 O—CH_3	Same as in dilaudid.	 O	*Dicodid* Less intense action than dilaudid.
Phenolic hydroxyl intact	 OH	Same as dilaudid except one hydrogen on ring 3 has methyl group.	 O	*Metopon* Less hypnosis but has equal analgesic potency as morphine

MORPHINE

HISTORY—Isolated from opium by Serturner in 1805



Cerebrospinal Axis—Preliminary central stimulation often causes excitement, followed by depression. Descending depression occurs.

Temperature Regulating Center—Depressed.

Respiratory Center—Depressed; threshold of cells to CO_2 increased; discharge of rhythmic impulse slowed

Vasomotor Center—No change Toxic doses depress.

Vomiting Center—Stimulated Nausea and vomiting common.

Cough Center—Depressed. Large doses abolish reflex.

Vagus Center—Stimulated May cause slowing of pulse.

Carotid Sinus—Depressed.

Sino-aortic Chemoreceptors—Remain active

Lungs—Respiratory rate decreased, tidal exchange slightly increased minute volume exchange decreased CO_2 output decreased total blood CO_2 and alveolar blood CO_2 increased. Bronchial musculature constricted Reduces clinical dyspnea by depressing vagal reflexes by reducing central perception.

Metabolism—Rate decreased 10%.

Adrenal—Epinephrine content depleted with large doses (anoxia)

Gallbladder—Smooth muscle tone increased. May enhance biliary spasm Atropine antagonizes spasm.

Liver—Function decreased for six hours (dye test) Glycogen depleted due to release of sympathin. Hyperglycemia of little significance except with large doses.

Kidney—*Function not significantly affected;* oliguria, followed by polyuria may occur

Ureters—Smooth muscle spasm occurs Increased tone, decreased motility Relieved by atropine.

Bladder—Urine retention may follow due to spasm of sphincter

Sphincters—Tone increased and defecation reflex obtunded.

Autonomic Effect—May behave like parasympathetic stimulant *Effects enhanced* by prostigmin.

Cord—Stimulated.

Peripheral Nerves—Not affected; hyperactive reflexes from stimulation of cord may result. No local analgesic action.

Cortex—Psychic sedation decrease of time sense merging into dreamless sleep. Threshold to pain perception raised. Removes psychic response to pain. Pain paths to consciousness interrupted. Motor areas unaffected by small doses, depressed by large doses. Perception and will unaffected. Deep coma with overdose.

Intracranial Pressure—Increased. *Respiratory depression with anoxia* further increases it.

Optic Thalamus—Analgesia. Dull pain obtunded. Large doses abolish all pain including visceral.

Eyes—Pupils constricted due to stimulation of motor (Edinger Westphal) nuclei. Dilate with asphyxia, active eyeball movements. Reflex remains active if antagonized by atropine.

Salivary Glands—Secretion decreased due to interference of reflex stimulation of gland.

Heart—Rate decreased (vagal); P R interval increased, no action on myocardium; rarely slight stimulation may occur

Blood Pressure—Affected only slightly with therapeutic doses. Usually reduced due to psychic sedation. May fall following postural changes due to depression of compensatory mechanisms.

Stomach—Motility decreased; emptying time increased; secretion of acid decreased, drug excreted in stomach.

Intestines—Activity decreased passage of chyme through bowel slowed. Secretions decreased. Absorption little affected Spasm and constipation frequent. Water more completely absorbed from the chyme.

Pancreas—Secretions diminished.

Uterus—Tone increased and contractions usually decreased drug passes through to fetus and often results in neonatal apnea.

Skeletal Muscles—Not affected. Stored temporarily in muscle. Muscle coordination not affected (motor cortex not depressed).

Blood—Combining power decreased lactic acid increased leukocytosis for 24 hours. Marked depression if acidosis is present.

Body Temperature—Falls due to depressed center dilated skin vessels and reduced metabolic rate.

Skin—Peripheral vessels dilate. Itching of nose may occur Urticaria not uncommon Sweating common. Not absorbed through unbroken skin.

Tolerance—Develops after repeated administration for 10 days to two weeks, necessitating larger doses to obtain desired therapeutic effect.

Addiction—Follows habituation and development of tolerance.

Elimination—10 to 15% eliminated unchanged in four or five hours. Stored temporarily in muscles Remainder conjugated by liver and excreted into urine in 24 to 36 hours. Traces found in urine, feces, and stomach contents Intravenous dose disappears in 10 to 30 minutes from blood. Stored in tissues.

PROPERTIES AND PREPARATIONS—An organic base. It is a white powder composed of fine needles which darken on exposure to air One gram dissolves in 5000 cc water It forms salts with many organic and mineral acids, most important of which is the sulphate. The sulphate is a white powder soluble in water (1 in 15.5 at 25°) It is partly soluble in alcohol and insoluble in chloroform and ether Morphine is included in the U.S.P XIII.

OPIUM ALKALOIDS AND THEIR DERIVATIVES

	Codeine	Heroin	Dilaudid	Dionin	Metopon	Papaverine	Apomorphine
History	Isolated by Robiquet in 1832.		Introduced by Knoll in 1926.		Developed by drug addiction committee.		
Chemistry	Methyl morphine occurs naturally. Also made by methylation of morphine.	Diacetyl morphine. Made synthetically by acetylation of morphine.	Dihydromorphinone	Ethyl morphine. Prepared synthetically by ethylation of morphine	A synthetic substance made from morphine. Methyl dihydromorphinone	Derived from opium. Contains no phenanthrene. Is an isoquinoline derivative.	Made by dehydration of morphine by heating with hydrochloric acid. Molecular rearrangement occurs.
Analgesic action	One-sixth of morphine.	Four to eight times as potent as morphine.	Ten times more potent than morphine.	Similar to codeine.	Twice as potent and similar to morphine but of shorter duration.	None	Negligible
Narcotic action	Mild. Large doses may even cause excitement. Increases spinal reflexes more than morphine	Causes euphoric contentment. Four to six times as potent as morphine	Four times more potent than morphine. Lasts shorter time than morphine.	Similar to codeine.	Less dulling of sensorium than with morphine.	None	Hypnotic in small doses. Produces an additive effect with other depressant
Metabolism	Slightly reduced. Increased by large doses.	Reduced more than with morphine.	Similar to morphine in comparable doses.	Similar to codeine.	Similar to morphine	Slight. May increase in large doses.	
Respiratory effects	Approximately one-fourth as potent as morphine in causing depression.	Over four or five times more depressing than morphine.	Similar to morphine in comparable doses.	Similar to codeine.	Little or no depression of respiration.	None. Little or no effect in relaxation of bronchial musculature.	Large dose causes collapse.
Circulatory effects	No remarkable effects.	Similar to morphine.	Similar to morphine in comparable doses.	Similar to codeine.	Similar to morphine but less intense.	None. Relaxes smooth muscles of blood vessels. Dilates coronaries.	Large dose may cause collapse
Effects in gastrointestinal tract	Causes spasm, constipation, etc. but less prominent than morphine.	Similar to, but considerably less, than morphine in proportional doses	Similar to morphine in comparable doses but less constipating	Similar to codeine.	Similar to morphine but less intense.	Relaxes smooth muscle.	Not Irritating. Causes emesis by central stimulation.
Biliary tract	Spasm of bile duct similar to morphine but less in extent and intensity		Spasm of bile duct but less intense in extent and intensity	Similar to codeine.		Relaxes smooth muscle.	
Ureter and bladder	Increased tone, decreased motility	Similar to morphine in proportional doses.	Similar to morphine in comparable doses.	Similar to codeine.		Relaxes smooth muscle.	Probably none.
Uterus	Depresses. Non-significant clinically. Less than morphine.	Similar to morphine in proportional doses.	Similar to morphine in comparable doses.	Similar to codeine.		None.	None.
Ocular response	Effects on vision less prominent than with morphine	Similar to morphine in proportional doses.	Similar to morphine in comparable doses.	Similar to codeine.	Less than morphine.	None.	None.
Emetic action	Present but less than with morphine	Less than morphine in proportional doses.	Somewhat less than morphine in comparable doses	Similar to codeine.	Less than morphine.	None.	Pronounced action. Stimulates vomiting center
Antitussive action	Present but less than with morphine.	More effective than morphine	Similar to morphine in comparable doses.	Similar to codeine.	Similar to morphine.	None.	None.
Elimination	Approximately 90% eliminated unchanged into urine.	Mostly eliminated unchanged in urine.		Similar to codeine.			Eliminated unchanged.
Tolerance	Occurs with repeated administration	Readily occurs with repeated administration.	Readily occurs with repeated administration.	Readily occurs with repeated administration.	Partly overcomes withdrawal symptoms of morphine.	None.	None.
Addiction	Occurs. Large doses required to produce euphoria.	Most addictive of morphine-like drugs.	Causes physical dependence. Less euphoria than with morphine.	Possesses mild addiction properties.	Mild addiction properties. Less addicting than most opium derivatives.	None.	None.
Preparations	Codeine (alkaloid) U.S.P. XIII. Codeine sulphate U.S.P. XIII. Tablets soluble 1:30 H_2O. Codeine phosphate soluble 1:2 H_2O (for injection)	Diacetyl morphine hydrochloride, but illegal to manufacture or import into the U.S. Not official.	Dihydromorphinone U.S.P. Prepared as the hydrochloride, white odorless crystalline water-soluble powder	White powder prepared as hydrochloride. Not official.	White powder prepared as hydrochloride. Not official.	White powder prepared as hydrochloride. Included in U.S.P. XIII.	Included in U.S.P. XIII.

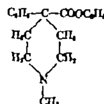
All foregoing drugs under supervision of Harrison Narcotic Act.

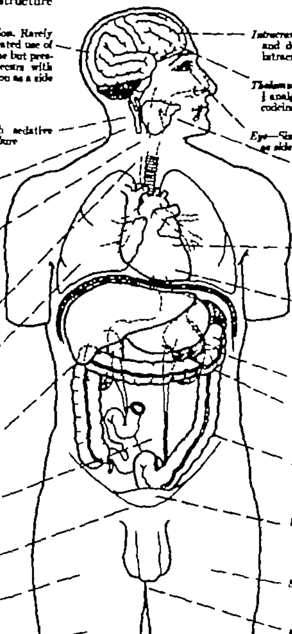
DEMEROL

HISTORY—Synthesized by Eisleb and Schaumann in Austria in 1939 as a substitute for atropine An analgesic spasmolytic and mild sedative agent.

SYNONYMS—Meperidine isonipecaine, dolantin pethidine

CHEMISTRY—A synthetic derivative of piperidine, (1 methyl, 4-phenylpiperidine 4-carbonic acid ethyl ester possessing the following structure





Cortex—Euphoria followed by mild depression. Rarely produces sleep. Tolerance may follow repeated use of drug Addiction liability less than morphine but present nevertheless. Drowsiness or sleep occurs with large doses. Dizziness and giddiness common as a side reaction.

Respiratory Center—Mild depression with sedative doses. Massive doses cause respiratory failure

Cough Center—Not depressed. Slight or no antitussive action.

Vomiting Center—Nausea and vomiting may follow rapidly injected intravenous doses or in ambulatory subjects Nausea and vomiting common in small number of cases regardless of route of administration

Vagus—Depressed. Drug possesses a mild atropine-like action.

Lungs—Little or no change in ventilation Respiration depressed by large doses Usually causes broncho-dilatation No effect on alveoli.

Gallbladder—Spasmolytic action May be useful in spasm of biliary ducts.

Ureter—Spasmolytic action causes decreased tonus. Direct depressant action on muscle reduces spasm

Bladder—Urinary retention uncommon

Skin—Pallor and sweating may occur as side reaction.

Blood—No changes in hematopoietic system. *No notable blood chemical changes.*

Intracranial Pressure—May increase Sluggish pupils and depression of respiration occur in presence of intracranial lesions.

Thalamus—Causes analgesia. Possesses approximately ⅒ analgesic action of morphine Potency lies between codeine and morphine

Eye—Size of pupil unchanged. Blurring of vision occurs as side reaction. *Dilatation of pupil with large doses.*

Salivary Gland—Moderate decrease in secretions. Dryness of mouth may occur as side reaction. Not as effective as atropine. Does not replace atropine in preanesthetic medication.

Heart—No effect in therapeutic doses. No changes in electrocardiogram. Pulse rate unchanged or increases slightly following therapeutic doses.

Blood Pressure—Usually no notable effect. *Transient hypotension may follow rapid* intravenous administration. Probably due to peripheral vasodilatation. No effect otherwise.

Spleen—Volume increased.

Stomach—Spasmolytic action Relaxes pyloric sphincter Delays gastric emptying time 50%.

Intestines—Decrease in motility due to spasmolytic action. Depresses smooth muscle fibres No constipating effects. Does not splint bowel.

Uterus—No appreciable reduction in activity or tone Drug passes into placental circulation. Large doses cause depression of fetal respiration.

Side Reactions—Frequent. Dizziness, nausea, vomiting, pallor More frequent in ambulatory subjects.

Elimination—Mostly unchanged. Approximately 75% of a therapeutic dose recovered in urine six to seven hours after administration.

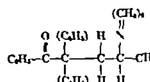
CLINICAL USES

As an analgesic orally 100 to 150 mgm. Intramuscularly 50 to 100 mgm. Intravenously 50 to 100 mgm slowly (side reactions frequent) Clinical use governed by Federal Bureau of Narcotics The drug causes addiction

ONSET OF ACTION—Twenty to sixty minutes. Analgesic potency lies between that of codeine (60 mgm.) and morphine (15 mgm.). Widely used as an obstetric analgesic in combination with barbiturates and scopolamine

PREPARATION—Demerol is a white crystalline substance slightly soluble in water with a strong alkaline reaction. Forms salts with mineral acids. For clinical use the hydrochloride is employed It is a white crystalline powder soluble in water melting at 187° Not decomposed by boiling.

METHADON



SYNONYMS—Adanon, amidone, dolophine, amidon.

CHEMISTRY—An aliphatic amino ketone (6 dimethyl amino-4-4 diphenyl-3 heptanone synthesized by the Germans during World War II. It is a synthetic basic compound which forms salts with acids. The most common salt is the hydrochloride. Its formula is

PHYSICAL PROPERTIES—White crystalline substance soluble in water and alcohol, insoluble in ether; melts at 230 to 235°C. Possesses a bitter taste.

Cortex—No significant effect. Large doses (10 mgm.+) cause depression. Does not allay apprehension. Euphoria with large doses. No effect on electroencephalogram. Large doses depress, cause slowing of cortical activity.

Respiratory Center—Depressed by moderate and large doses.

Vagus Center—Stimulated. Slows the heart.

Vomiting Center—Nausea and emesis occurs as side reaction particularly with large doses.

Cough Center—Depressed. Acts as antitussive.

Vagus Nerves—Causes hyperactivity which is antagonized by atropine.

Lungs—Minute volume exchange reduced approximately 15% with therapeutic doses.

Liver—Cephalin flocculation, blood bilirubin remains unchanged after successive daily doses.

Kidney—Urinary output reduced. Antidiuretic action lasts several hours.

Ureter—Spasmogenic action. Caused by parasympathetic action.

Blood—No change in blood sugar or N.P.N. No effect on total number of morphology of W.B.C. or R.B.C. Total counts unchanged over prolonged periods of administration.

Elimination—Approximately 85% of 7.5 mgm. oral dose eliminated unchanged. Remainder detoxified. Exact fate not known.

Thalamus—Increase in pain threshold.

Eye—Miosis in large doses.

Salivary Glands—Stimulated. Secretions may be increased.

Heart—Pulse rate slowed. E.K.G. shows sinus bradycardia and prolongation of QRS Complex (vagal effect). Abolished by atropine.

Blood Pressure—No effect or slight lowering of systolic pressure.

Intestine—Increases muscle tone. Propulsive activity decreased. Spasmogenic action caused by parasympathetic stimulation. Locally causes a spasmolytic action.

Uterus—Drug passes through placenta. Fetal respirations depressed.

Addiction—Relieves the morphine abstinence syndrome in addicts. Tolerance develops after prolonged administration followed by withdrawal symptoms.

CLINICAL USES

For Preoperative Medication—Does not allay apprehension. Suitable only when combined with sedatives such as barbiturates.

For Postoperative and Other Pain—An analgesic comparable to morphine in potency.

Dosage—Oral 2.5 to 10 mgm.—average dose 5 mgm.—effect becomes established within 30 to 60 minutes. Intramuscularly—2.5 to 10 mgm. Effect becomes established in 20 to 30 minutes. Intravenously 2.5 to 10 mgm. Effect becomes established within 5 minutes.

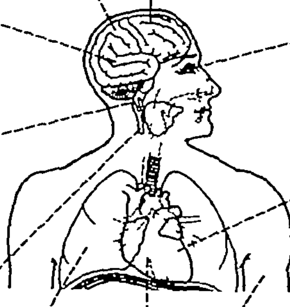
SYNTHETIC NARCOTIC ANALGESICS

Name	Levorphan	Alphaprodine	Anileridine	Phenazocine
Synonym	*Dromoran, Levo-dromoran*	*Nisentil*	*Leritine.*	*[illegible] NIH-7519, Prinadol*
History	Introduced in [illegible]	Prepared by Randall & Lehmann 1948	Prepared by Merck 1957	Synthesized by E. L. May National Institutes of Health U.S. [illegible]
Chemistry	1-3 hydroxy N-methyl morphinan. Lacks oxygen bridge, alcoholic hydroxyl group and double bond between carbons 7 & 8 of morphine. Has d & l form	1,3,dimethyl 4,phenyl 4,piperidyl propionate. Allied to meperidine except has propionoxy group instead of esterified carboxy linkage. Forms hydrochloride.	Similar to meperidine except nitrogen atom bears $-C_2H_4-$(ring)$-NH_2$ group instead of NH_3. Forms phosphate instead of hydrochloride. Ethyl 1(4 aminophenyl) 4 phenyl isonipecotate.	2-hydroxy 5, 9 dimethyl 2-phenyl ethyl 1-6-7 benzomorphan. White powder M.P. [illegible]°C. D & L form. Both forms active. Levo [illegible]X potent than dextro.
Analgesic action	Levo compound active, dextro not. 4–8 times more potent than morphine. Maximal effect in 1–1½ hrs. Lasts 4–8 hrs.	Shorter acting but more intense effect than meperidine but less than morphine.	Intermediate between meperidine and morphine. [illegible] times greater than meperidine, ½ as potent as morphine.	[illegible] to 10X more potent than morphine
Narcotic or hypnotic action	4–8 times more potent than morphine. Hypnotic effect not quite so pronounced. Dextro isomer no effect. Offers little or no advantage over morphine.	Less intense than and shorter acting than morphine.	Less than morphine. Similar to meperidine. Duration approximately 4 hrs.	Less than morphine. Excitement uncommon. E.E.G. pattern similar to normal sleep.
Effects on respiration	Depresses similar to morphine in comparable doses. Antagonized by nalorphine or levallorphan.	Depresses but less than morphine. Antagonized by nalorphine or levallorphan.	Depresses respiration more than meperidine but less than morphine. Causes fetal depression. I.V. administration of 10 mg. or more causes apnea. Antagonized by nalorphine and levallorphan.	Slows rate. Depressed but not to same extent as morphine. Same decrease in tidal volume in [illegible] mgm. dose.
Circulation effects	Similar to morphine in comparable doses.	Similar to but less intense than morphine.	Hypotension follows rapid I.V. injection or [illegible].	Some bradycardia. Same effects as morphine but less cardiac output. Not depressed.
Gastrointestinal effects	Similar to morphine in comparable doses	Similar to morphine—spasmogenic.	Spasmolytic effect like meperidine. Opposite to morphine.	
Biliary tract	Similar to morphine	Similar to morphine.	Similar to meperidine.	
Urinary effects	Similar to morphine.	Similar to morphine.	Similar to meperidine.	
Uterus	Similar to morphine	Passes into fetal circulation.	Similar to meperidine. Some slowing of labor	Passes through placental barrier
Ocular response	Similar to morphine	Similar to morphine.	Similar to meperidine.	
Emetic effect	Qualitatively similar to morphine, quantitatively less.	Does not occur unless ambulation occurs.	Ordinarily not seen except in ambulation.	None. Even has an anti-emetic effect
Antitussive effects	Similar to morphine. Dextro derivative active also.	Similar to morphine.	Possesses an antitussive effect.	
Elimination	Conjugated in liver [illegible]% excreted as glucuronide slowly ([illegible] days).	Completely detoxified in body	Partly detoxified by liver and partly eliminated unchanged.	Antagonized by nalorphine.
Tolerance and addiction	Similar to morphine. Tolerance develops as rapidly. Under Harrison Narcotic Law	Tolerance develops. Addiction liability less than morphine. Under Harrison Narcotic Law	Tolerance develops after repeated doses. Addiction liability equivalent to morphine. Suppresses morphine abstinence completely. Meperidine does not. Dose equivalent to meperidine sustains addiction.	Appears to have addicting qualities but far less than morphine.
Preparation	2 mgm. tablets or 2 mgm. per cc. for I.M. use. Dose [illegible] mgm	40–60 mgm. I.M. May be used slowly I.V. Not used orally	40–[illegible] mgm. I.M. Effective orally [illegible]–75 mgm. Duration [illegible] hrs.	Sterile 10 cc. 1.0 mgm./cc. Dose .5 to [illegible] mgm. I.M. Dose .5 to [illegible] mgm. I.V.

ANTINARCOTICS—NALORPHINE (NALLINE)

HISTORY—Synthesis and pharmacologic actions first described in 1942 by Weijlard and Erickson. Hiller (1943) and also Unna noted that the compound antagonized the action of morphine in animals. Hart and McCauley (1944) reported additional studies confirming Unna's findings. Huggins and co-workers (1950) and Smith, and Lehman reported experimental studies in man. Possibility that an antidote might be found first indicated by Pohl (1914) who noted that N-allyl-nor-codeine antagonized morphine.

DESCRIPTION—*Chemical* name is N-allyl-normorphine. Nalorphine is a congener of morphine. A methyl group on the nitrogen atom is replaced by an allyl group. The drug is not a stimulant or convulsant. It is a narcotic far more feeble than morphine.



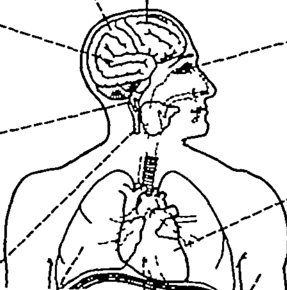
SYNTHETIC NARCOTIC ANALGESICS

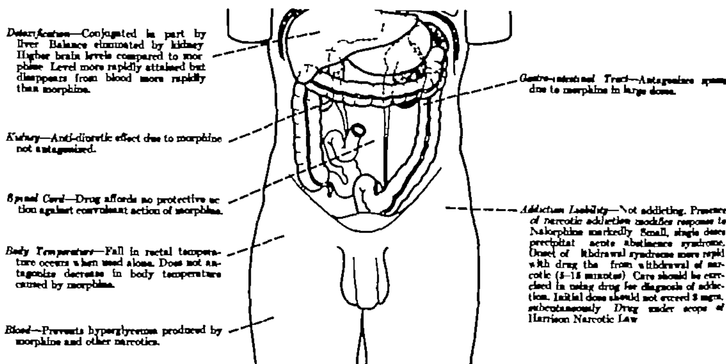
Name	Levorphan	Alphaprodine	Anileridine	Phenazocine
Synonym	Dromoran, Levo-dromoran	Nisentil	Leritine	AX-[illegible], NIH-7519 Prinadol
History	Introduced in 194[illegible].	Prepared by Randall & Lehmann 1948	Prepared by Merck 1957	Synthesized by E. L. May National Institutes of Health U.S. 19[illegible].
Chemistry	l-3 hydroxy N-methyl morphinan. Lacks oxygen bridge, alcoholic hydroxyl group and double bond between carbons 7 & 8 of morphine. Has d & l form.	1,3-dimethyl 4-phenyl 4-piperidyl propionate. Allied to meperidine except has propionoxy group instead of esterified carboxy linkage. Forms hydrochloride.	Similar to meperidine except nitrogen atom bears $-C_2H_4$–⬡–NH_2 group instead of NH_3. Forms phosphate instead of hydrochloride. Ethyl 1(4 aminophenyl ethyl) 4 phenyl isonipecotate.	2-hydroxy 5,9 dimethyl 2-phenyl ethyl 6,7 benzomorphan. White powder M.P. [illegible]°C. D & L form. Both forms active. Levo 60X potent than dextro.
Analgesic action	Levo compound active, dextro not. 4–6 times more potent than morphine. Maximal effect in 1–1½ hrs. Lasts 4–6 hrs.	Shorter acting but more intense effect than meperidine but less than morphine.	Intermediate between meperidine and morphine. 3½ times greater than meperidine, ⅓ as potent as morphine.	3 to 10X more potent than morphine.
Narcotic or hypnotic action	4–6 times more potent than morphine. Hypnotic effect not quite as pronounced. Dextro isomer no effect. Offers little or no advantage over morphine.	Less intense than and shorter acting than morphine.	Less than morphine. Similar to meperidine. Duration approximately 4 hrs.	Less than morphine. Excitement uncommon. E.E.G. pattern similar to normal sleep.
Effects on respiration	Depresses similar to morphine in comparable doses. Antagonized by nalorphine or levallorphan.	Depresses but less than morphine. Antagonized by nalorphine or levallorphan.	Depresses respiration more than meperidine but less than morphine. Causes fetal depression. I.V. administration of 10 mg. or more causes apnea. Antagonized by nalorphine and levallorphan.	Slows rate. Depressed but not to same extent as morphine. Some decrease in tidal volume in 2 mgm. dose.
Circulation effects	Similar to morphine in comparable doses.	Similar to but less intense than morphine.	Hypotension follows rapid I.V. injection or ambulation.	Some bradycardia. Same effects as morphine but less cardiac output. Not depressed.
Gastrointestinal effects	Similar to morphine in comparable doses.	Similar to morphine—spasmogenic.	Spasmolytic effect like meperidine. Opposite to morphine.	
Biliary tract	Similar to morphine.	Similar to morphine.	Similar to meperidine.	
Urinary effects	Similar to morphine.	Similar to morphine.	Similar to meperidine.	
Uterus	Similar to morphine.	Passes into fetal circulation.	Similar to meperidine. Some slowing of labor	Passes through placental barrier
Ocular response	Similar to morphine.	Similar to morphine.	Similar to meperidine.	
Emetic effect	Qualitatively similar to morphine, quantitatively less.	Does not occur unless ambulation occurs.	Ordinarily not seen except in ambulation.	None. Even has an anti-emetic effect.
Antitussive effects	Similar to morphine. Dextro derivatives active also.	Similar to morphine.	Possesses an antitussive effect.	
Elimination	Conjugated in liver. 15–60% excreted as glucuronide slowly (3–6 days)	Completely detoxified in body	Partly detoxified by liver and partly eliminated unchanged.	Antagonized by nalorphine.
Tolerance and addiction	Similar to morphine. Tolerance develops as rapidly. Under Harrison Narcotic Law	Tolerance develops. Addiction liability less than morphine. Under Harrison Narcotic Law	Tolerance develops after repeated doses. Addiction liability equivalent to morphine. Suppresses morphine abstinence completely. Meperidine does not. Dose equivalent to meperidine satisfies addiction.	Appears to have addictive qualities but far less than morphine.
Preparation	2 mgm. tablets or 2 mgm. per cc. for I.M. use. Dose 2–3 mgm.	40–60 mgm. I.M. May be used slowly I.V. Not used orally	40–60 mgm. I.M. Effective orally 50–75 mgm. Duration 2–4 hrs.	Sterile 10 cc. 1.0 mgm./cc. Dose .3 to 2 mgm. I.M. Dose .1 to 1.0 mgm. I.V.

ANTINARCOTICS—NALORPHINE (NALLINE)

HISTORY—Synthesis and pharmacologic actions first described in 1942 by Weijlard and Erickson. Hiller (1943) and also Unna noted that the compound antagonized the action of morphine in animals. Hart and McCauley (1944) reported additional studies confirming Unna's findings. Huggins and co-workers (1950) and Smith, and Lehman reported experimental studies in man. Possibility that an antidote might be found first indicated by Pohl (1914) who noted that N-allyl-nor-codeine antagonized morphine.

DESCRIPTION—Chemical name is N-allyl-normorphine. Nalorphine is a congener of morphine. A methyl group on the nitrogen atom is replaced by an allyl group. The drug is not a stimulant or convulsant. It is a narcotic far more feeble than morphine.





Onset and Duration of Action—Usually with 2–3 minutes, less than 15 minutes. Response lasts from 1½ to 4 hours. Does not antagonize mild respiratory depression. May even enhance it. Injected into umbilical vein antagonizes respiratory depression in asphyxiated babies born of mothers treated with narcotics. Pre-treatment of severely depressed mother before birth prevents or decreases asphyxia of newborn.

Combinations with Narcotics—(10 mgm. morphine, 2 mgm. Nalorphine) Gave depressant effects equal to 15 mgm. morphine. Indistinguishable from morphine alone. Response to CO_2 and minute volume same.

Dosage—5 mgm. intravenously repeated after 2–3 minutes until 15 mgm. are administered. Failure to obtain some response with 15 mgm. is presumptive evidence depression is due to non-narcotic substances. Doses exceeding 15 mgm. ordinarily not necessary. 0.1 to 0.5 mgm. by umbilical vein for newborn. 0.75–1 mgm. per 10 lbs. body weight for children

Antagonism to Other Drugs—Does not antagonize thiopental, hexobarbital and other barbiturates or hypnotic of non-barbiturate type or the volatile anesthetics.

Preparation—1cc. ampules containing 5 mgm. per cubic centimeter

LEVALLORPHAN

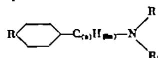
DESCRIPTION—Levallorphan is N-allyl-dromoran. It is a counterpart of dromoran with the methyl group replaced by an allyl group. It is approximately 3 to 5 times more potent than Nalorphine. It exerts the same pharmacologic effects. Does not come under the scope of the Harrison Narcotic Law.

DOSE—Adults 2 mgm. is equivalent to 5 mgm. of Nalorphine. For infants 1/10 to ½ mgm. is usual dose.

SECTION XI LOCAL ANESTHETICS

LOCAL ANESTHETICS

Local anesthetics (cocaine and other alkaloids derived from coca plant excepted) are synthetic aromatic or heterocyclic compounds. Two large groups may be differentiated one composed of non-nitrogen containing alcohols, the other composed entirely of nitrogenous compounds. These conform to a general structure composed of a primary secondary or tertiary amine and an aromatic nucleus (usually an acid) separated by an intervening side chain thus



Radicals may be substituted on various positions of the aromatic nucleus. The amine may be primary secondary or tertiary

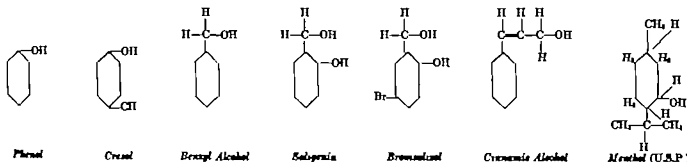
The alcohols are suitable for topical use and are non-injectable They exert their action by virtue of being protoplasmic irritants.

The injectable local anesthetics are nitrogenous derivatives and of the type i the second group. The majority of this group are esters. A few are amides and other miscellaneous types. Their classification chemically is as follows

Local anesthetics
- alcohols—phenol, menthol, benzyl alcohol, etc.
- nitrogenous bases
  - esters—cocaine procaine metycaine, etc.
  - miscellaneous group—nupercaine holocaine, quinine

Physical agents such as cold, pressure electricity induce local anesthesia, but are limited i clinical usefulness.

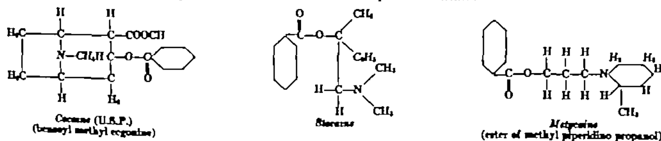
Alcohol Group—Both aromatic alicyclic and heterocyclic alcohols comprise this group. Aliphatic alcohols are of little importance as local anesthetics. They are liquids, contain no nitrogen, are neutral or acid in nature moderately soluble in water Benzyl alcohol is the most widely used The following alcohols belong in this group:



Phenol — *Cresol* — *Benzyl Alcohol* — *Saligenin* — *Bromsaligenol* — *Cinnamic Alcohol* — *Menthol* (U.S.P.)

Ester Group—This group is the largest, the most important, and includes most of the drugs in current use Structurally each is composed of an acid an alcohol, upon which is one or more nitrogen toms usually in the form of a tertiary amine The amine may be on the alcohol portion, the acid portion or both The acid is usually aromatic in nature Esters are basic, form water-soluble salts with acids. Esters may be classified according to the acid from which they are formed

Benzoic Acid Esters—Benzoic acid, the simplest aromatic acid is esterified with complex amino alcohols.

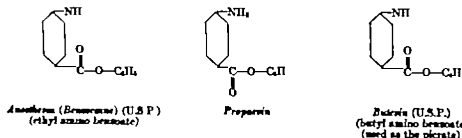


Cocaine (U.S.P.)
(benzoyl methyl ecgonine)

Stovaine

Metycaine
(ester of methyl piperidino propanol)

Para-amino Benzoic Acid Esters—1 Slightly soluble type Formed from simple aliphatic alcohols. Possess low toxicity Useful for surface anesthesia only



Anesthesin (*Benzocaine*) (U.S.P.)
(*ethyl amino benzoate*)

Propaesin

Butesin (U.S.P.)
(butyl amino benzoate)
(used as the picrate)

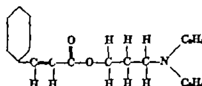
2. Soluble type (very important group) Formed from complex amine aliphatic alcohols.

Amino Group — Acid — Alcohol — Amino Group

$H-N-C_6H_4-C(=O)-O-(CH_2)N<$

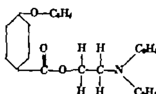
	Amino Group	Alcohol	Amino Group	Amino Group
Procaine	$-H$	$-CH_2-CH_2$	$-C_2H_5$	$-C_2H_5$
Butyn	$-H$	$-CH_2-CH_2-CH_2$	$-C_4H_9$	$-C_4H_9$
Pontocaine	$-C_4H_9$	$-CH_2-CH_2$	$-CH_3$	$-CH_3$
Larocaine	$-H$	$-CH_2-C(CH_3)(CH_3)-CH_2$	$-C_2H_5$	$-C_2H_5$
Tutocaine	$-H$	$-CH(CH_3)-CH(CH_3)-CH_2-$	$-CH_3$	$-CH_3$
Isocaine	$-H$	$-CH_2-CH_2$	$-C_3H_7$ (Iso)	$-C_3H_7$ (Iso)
Monocaine	$-H$	$-CH_2-CH_2$	$-C_4H_9$ (Iso)	$-H$
Amylcaine	$-H$	$-CH_2-CH_2$	$-C_5H_{11}$	$-H$

Cinnamic Acid Esters—



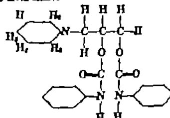
Apothesine (N. N. R.)
(diethylamino propanol ester)

Para Ethoxy Benzoic Acid Esters—



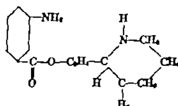
Intracaine
(diethylamino ethanol ester)

Carbamic Acid Esters—



Diothane (N. N. R.)
(piperidine propandiol diphenyl urethane)

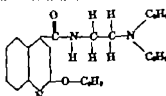
Ortho Amino Benzoic Acid Esters—



Locaine

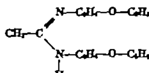
Miscellaneous Groups—Drugs in this group are compound products, not esters.

Quinoline Derivatives—



Nupercaine (N. N. R.)
(butyl oxy-cinchoninic acid—diethyl ethylene diamide)

Para Ethoxy Aniline Derivatives—



Holocaine (U. S. P.)
Phenacaine (U. S. P.)
(ethenyl diethoxy-diphenyl amidine)

Quinine Derivatives—

Eucupin, most important, is isoamyl ether of hydrocupreine (capable of prolonged anesthesia)

PROPERTIES—The nitrogenous local anesthetics are basic, bitter compounds. Many are powders, some are oily liquids. Local anesthetics are prepared as salts of hydrochloric, sulphuric and other acids. The acid used to form the salt is selected from the standpoint of solubility. Salts are crystalline, water soluble, and acid in reaction. Alkalis precipitate the free base from aqueous solutions of the salt. Bases are more soluble in oils and organic solvents than in water. They will reform salts from acids. Bases are less stable than the salts. Local anesthetics respond to many reactions of alkaloids and yield precipitates with alkaloidal reagents and salts of heavy metals, such as mercury and silver. Many local anesthetics decompose upon boiling, by the action of light, air, moulds, and other agents. Salts of local anesthetics hydrolyze to a variable extent in aqueous solutions, depending upon the structure of the molecule and the acid forming the salt.

BIOLOGICAL EFFECTS OF LOCAL ANESTHETICS

Local anesthetics in sufficient concentrations (1) affect all cells (2) have a special predilection for nerve tissue (3) have a reversibility of action They exert their effect by blocking conduction when applied at any single point in a neuron

Colloids—Ultra microscopic flocculation of protein occurs. Action is reversible Cell function restored to normal after removal of drug.

Lipoids—Free base more soluble in lipoids than water Affinity for and effect on nerve tissue may be partly due to lipoid solubility

Ions—Potassium ions diffuse from within outward and concentrate on cell surface

Metabolism—Oxygen consumption reduced. Carbon dioxide output decreased. Ammonia output reduced.

Electrical Phenomenon—Drug interferes with bility of nerve to become depolarized as action potential traverses nerve fibre A blockade of nerve impulses occurs as potential arrives at site of pplication of drug on fibre.

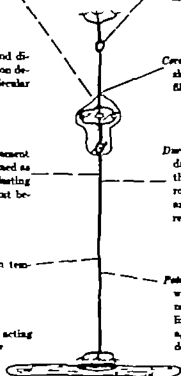
Permeability of Cell Membrane—Usually decreased. Unionized molecules of salt diffuse into cell.

Adsorption—Base and ions of salt are adsorbed to negatively charged particles in vitro. Similar response may occur in vivo.

Surface Tension—Lowered in vitro by many drugs. Similar effects may occur in vivo lowering interfacial tension in colloid systems.

Osmosis—Hyper and hypotonic solutions alter osmotic pressure if injected in tissues and cause crenation or swelling of cells.

FACTORS INFLUENCING DURATION AND INTENSITY OF BLOCKADE BY LOCAL ANESTHETICS



Site of Application—Blockade occurs at sit of application only Effective anywhere in the neuron, along portion of the axon, dendrite or cell body

Configuration of Molecule—Potency and duration depend directly upon ease of diffusion into nerve tissues. Diffusion depends upon physical properties induced by molecular configuration

Concentration—Latent period is time interval between moment of application and establishment of blockade (Shortened as concentration increases.) Interval greater with longer lasting drugs. Concentration increases duration up to a point beyond which it is little affected.

Temperature—Onset of action hastened by increase in temperature of injected solution.

Elimination—More rapidly detoxified drugs are shorter acting due to rapid decrease of concentration in nerve tissue

Fiber Size—Smaller fibres (sensory and autonomic) affected before large (motor) Selectivity is a function of fibre size and not due t chemical composition of nerve

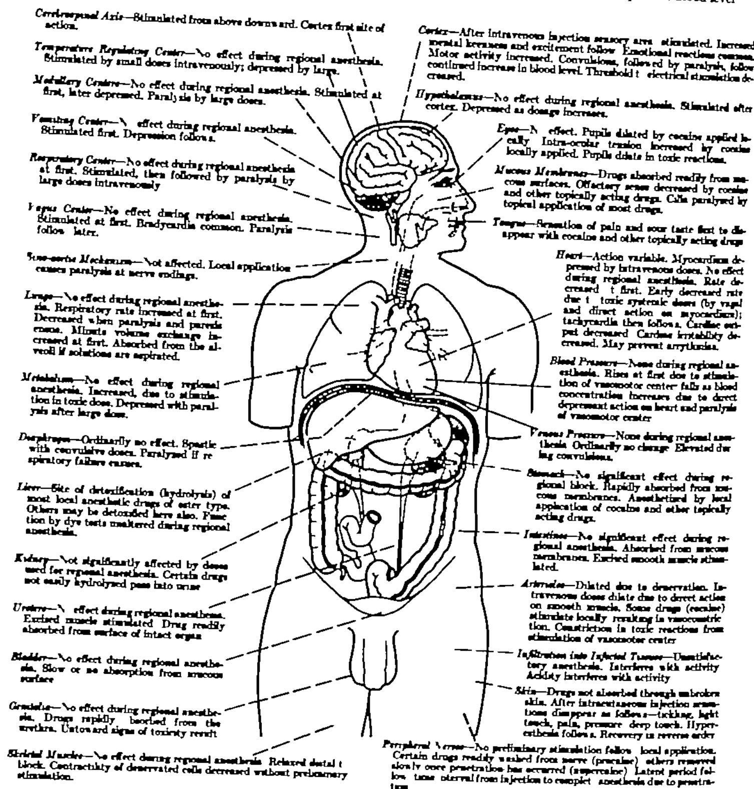
Covering—Penetration more rapid into unmyelinated unsheathed fibers; action potential disappears first. Myelinated fibers without sheaths affected before those with sheaths.

Duration of Contact—Depends upon the ease of elimination of drug from site of application. The more rapid the removal the shorter the duration. Influenced by vascularity surrounding site of injection. Longer contact allows penetration and sustained concentration in nerves. Epinephrine inhibits removal.

Potentiating Agents—Non-anesthetic drugs enhance action when combined with the agent. Purines (caffeine theobromine et .) dyes (methylene blue) proteins (albumin, globulin, glutens, etc.) ions (potassium, calcium) alkalinizing agents (bicarbonates, carbonates), are effective to various degrees.

GENERAL SYSTEMIC EFFECTS OF LOCAL ANESTHETICS

Local anesthetics are absorbed from site of injection and carried to liver kidney and muscles in blood Circulating drug gives rise to certain systemic responses, the nature and intensity of which depend upon the blood level of the drug.



TOXICITY OF LOCAL ANESTHETICS

Two types of toxicity to local anesthetic drugs are recognized (1) Local toxicity—direct damage to tissues at the site of application, (2) systemic toxicity—caused by the drug circulating in the plasma Ultimately all of a local anesthetic passes from the site of injection or topical application into the blood Rapid absorption results in high plasma levels and syndromes of systemic toxicity

FACTORS INFLUENCING LOCAL TOXICITY

1. Inherent nature of drug. All local anesthetics are protoplasmic poisons capable of causing death of tissue by dehydration or chemical alteration of cellular protein if used to excess.
2. Solubility of drug. Certain drugs precipitate at pH of tissues. Precipitate acts as foreign body
3. Concentration of drug Concentrated solution of normally non-injurious drug apt to cause local damage

TYPES OF SYSTEMIC TOXICITY

1. Intoxication
   (a) Intolerance—Normal quantities result in symptoms of over dosage.
   (b) Overdosage—Use of excess quantities.
2. Allergic
   (a) Anaphylaxis—Sudden circulatory collapse.
   (b) Antigen antibody type—Eczema, urticaria, bronchospasm, laryngeal edema
3. Idiosyncrasy—Response not ordinarily expected or characteristic of the drug.

FACTORS INFLUENCING SYSTEMIC TOXICITY

1. Potency of drug An increase in potency of a drug do not necessarily parallel increase in toxicity Dosage must be scaled in proportion to potency of reference drug (Tetracaine 1 mgm. = procaine 10 mgm.)
2. Concentration of drug. Concentrated solutions absorbed more rapidly than dilute from site of application. Least concentrated effective solution should be employed.
3. Vascularity of tissue Rapidity of absorption increases with degree of vascularity Vasoconstrictors inhibit absorption in highly vascular areas Hyaluronidase promotes spreading and facilitates absorption.
4. Blood level Varies with rate of absorption from a given site, vascularity and total dose Rapid increase to a plasma level induces convulsions.
5. Rate of elimination or detoxification. Rapidly and more easily detoxified drugs are toxic

TYPES AND SYSTEMS OF SYSTEMIC REACTIONS

Systems vulnerable to high plasma levels

1. *Central Nervous System*
   (a) Causes stimulation (characterized by excitement, delirium, nausea, vomiting, convulsions) This is followed by paralysis (coma, respiratory failure) if dose is large.
   (b) Causes depression without stimulation (characterized by coma)
2. *Cardiovascular System*
   (a) Causes myocardial depression (hypotension, bradycardia)
   (b) Causes vasodilatation from smooth muscle depression or vasomotor center depression (characterized by hypotension, bradycardia)
   (c) Combination of a and b
3. *Combined Vascular and Central Nervous System* (1 & 2)

METHOD OF TESTING SYSTEMIC TOXICITY

1. Intravenous injection. Drug injected rapidly at a constant rate into animals until convulsions occur Procaine drug of reference Absolute toxicity = milligrams causing convulsions divided by milligrams procaine producing same effect in same time under identical conditions.
2. Intraperitoneal injection. An index rate of absorption and effects produced by a single dose.
3. Subcutaneous injection. An index of diffusibility Permits study of varying concentration and effect of vascularity on absorption.

TREATMENT OF SYSTEMIC TOXIC REACTIONS

1. *For prophylaxis.* Prevention is better than cure. Systemic reactions from local anesthetics are lethal. In order to avoid reactions:
   (a) use least amount of drug necessary to produce blockade
   (b) use weakest solution possible.
   (c) attempt aspiration while injecting drug to rule out placement in vessel
   (d) use vasoconstrictors to retard absorption.
   (e) use short-acting barbiturate (secobarbital 100 mgm.) for premedication one hour prior to injection of drug
2. *For convulsions* Barbiturates I V Ultra short-acting barbiturates (thiopental, thiamylal, etc.) most effective Short-acting second best. Long-acting suitable in absence of short-acting
3. *For respiratory failure* Artificial respiration. Analeptics of no benefit.
4. *For circulatory collapse* Restore blood pressure with sympathomimetic amines (ephedrine, phenylephrine (neosynephrine) or methoxamine (Vasoxyl)
5. *For cardiac arrest* (Asystole)—cardiac massage

CHARACTERISTICS OF ALLERGIC RESPONSES

1. *Antigen—antibody type.* Cutaneous manifestations wheezing, urticaria, eczema, bronchospasm occur after repeated exposure to drug. Cross sensitization possible (e g procaine, benzocaine) Use antihistamines.
2. *Anaphylactoid.* Sudden circulatory collapse after injection or application of infinitesimal quantity of drug. No previous exposure. Probably due to histamine release. Treat for circulatory collapse and respiratory failure

CHARACTERISTICS OF INTOLERANCE

1. Less than accepted quantity of drug produces signs of overdosage occurs in aged debilitated patients. Treatment as for overdosage

CHARACTERISTICS OF IDIOSYNCRASY

1. Normal response not ordinarily expected of drug—such as tachycardia, hypertension, hallucinations, etc Treatment symptomatic

ABSORPTION AND SYSTEMIC TOXICITY

Subcutaneous Tissue (Scalp)—Highly vascular. Absorbed rapidly. Anesthesia of brief duration unless vasoconstrictors are added to retard absorption.

Barbiturates do not influence rate of absorption.

Subcutaneous Tissue—(*Average vascularity*) Absorbed gradually. Level curves barely detectable. Peak reached in 10–20 minutes. Vasoconstrictors retard absorption. Epinephrine 1:100,000 most effective agent. Nor-epinephrine effective, but may cause slough from intense vasoconstriction. Hyaluronidase promotes spreading. Increases blood level.

Skin—No absorption from unbroken skin. Absorbed from abraded skin surface from aqueous solutions, suspensions of free base or water soluble ointments. No absorption when applied to 1st and 2nd degree burns. Absorbed from broken blisters of 3rd degree.

Serous Surfaces—Rapidly absorbed from peritoneal and pleural surfaces. Blood levels comparable to those of rapid intravenous injection follow intraperitoneal injection.

Bone Marrow—Similar to intravenous injection. Rapid rise in plasma level.

Intra-arterial—Drug passes into and partially stored in tissues. Application of tourniquets to an extremity prevent passage of drug into venous circulation. Regional anesthesia of extremity results.

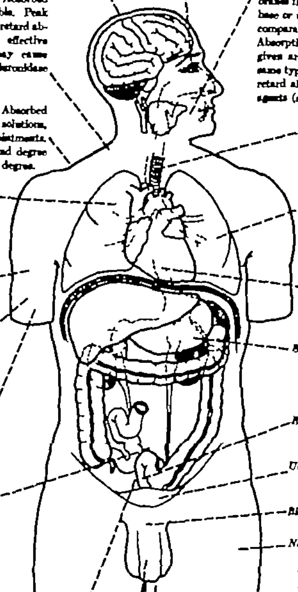
Intravenous—Plasma level proportional to rate of injection of given dose. Barely detectable levels follow slow infusion (1% procaine—1 gm per hour). Rapid injection results in abrupt rise and steep plasma levels—severe reactions.

Spinal Canal—Passage into blood slower than from other areas of body. Blood levels seldom detectable following doses used for spinal anesthesia. Vasoconstrictors retard absorption and increase duration 50% or more. In order of decreasing effectiveness are: epinephrine, norepinephrine, pitressin, phenylephrine (neosynephrine). Ephedrine, oenethyl, methoxamine ineffective. Systemic pressor responses uncommon following intratracheal injection of mixtures.

Peridural Space—Drug diffuses along nerves through intravertebral foramina. Absorption curves follow similar patterns to subcutaneous. Vasoconstrictors retard absorption.

Cavernous Tissue—Drug absorbed from venous sinuses.

Lymphatics—Part of drug passes from tissues spaces into lymph and thence into venous system after infiltration.



Eye—Absorbed through conjunctional membranes from aqueous solutions. Blood levels not detectable. Conjunctival injection follows use of hypertonic solutions or in allergic states.

Pharynx—Readily absorbed through mucous membranes from aqueous solutions of salts, suspensions of base or water soluble ointments. Plasma level curves comparable to those of slow (2 mins) I.V. injection. Absorption depends upon total weight applied to a given area and not concentration. 1 cc. 4% yields same type curve as 2 cc. 2%. Vasoconstrictors do not retard absorption from mucous membranes. Drying agents (atropine) do not retard absorption.

Trachea and Bronchi—Absorption similar to but more rapid than from pharynx. Peak levels high and more quickly attained.

Alveoli—Hydrostatic forces designed to draw fluids from alveoli into capillaries to maintain "dry lung." Rapid absorption follows instillation or inhalation of nebulized solutions.

Oesophagus—Poorly absorbed from this site. Barely detectable blood levels result.

Stomach—Plasma levels low. Drugs probably hydrolyzed in passage through liver from portal system.

Rectum—Absorbed from mucosa of anal canal.

Urethra—Significant blood levels. Hazards of absorption increase if membrane is traumatized from instrumentation.

Bladder—Not absorbed from this site.

Nerve—Drug penetrates into axone dendrite or cell body. Hydrocarbon pole (lipophilic) orients itself into lipoid phase. Amine group (hydrophilic) orients into aqueous phase.

Gradient established from tissue fluid into axone by deposition of drug perineurally.

Drug enters axonal membrane (at node of Ranvier only in myelinated fibers). Stabilizes membrane. K and N unable to migrate in or out. Depolarization and repolarization necessary for propagation of action current to transmit nerve impulse does not occur.

RECOVERY:

Peri-axonal concentration of anesthetic declines as drug passes into lymph. Gradient reversed: drug passes from axone to lymph. Permeability and function restored.

	Procaine (U.S.P.)	Pontocaine	Tutocaine	Larocaine
Synonyms	Ethocaine Planocaine Neocaine Novocaine Allocaine Scurocaine	Pontocaine (N.N.R.) Tetracaine (U.S.P.) Amethocaine Pantocaine	Butamin.	
Chemical nature	Para amino benzoic acid ester of diethyl amino ethanol.	Para butyl amino benzoic acid ester of dimethyl amino ethanol.	Para amino benzoic acid ester of dimethyl amino methyl butanol.	Para amino benzoic acid ester of 2 dimethyl, 3 diethyl propanol.
Properties	Base—white colorless, bitter powder M.P 60 to 61 Sl. sol. in H_2O. Soluble alcohol chloroform. Hydrochloride M.P 153 to 156° One gm. dissolves in 6 cc. H_2O Solution has pH 6.0.	Base—white, colorless, bitter powder Sl. sol. in H_2O Hydrochloride M.P 134 to 135°C. Sol. 1 in 7 H_2O at 25°C Easily precipitated by weak bases and carbonates.	Hydrochloride Light ivory colored, odorless, bitter powder M.P 212 to 215 Sol. 1 in 4 H_2O	Hydrochloride Whit powder M.P 196 to 197° Sol. 1 in 2 H_2O and 10 alcohol.
Prepared by	Einhorn 1905.	Eisleb 1932.	Schulemann 1928.	Mannich 1930.
Potency	Procaine is standard for comparison of other local anesthetic drugs.	Approximately 10 times greater than procaine in man.	Somewhat greater than procaine Topically two to four times greater than cocaine	Approximately four times greater than procaine
Toxicity	Not known for man. Administered intravenously over one hour One gram easily tolerated.	Relative toxicity equals procaine. Absolute toxicity approximately 10 times greater than procaine	Two to four times greater than procaine	Two and one half times greater than procaine
Detoxification	Hydrolyzed in liver to para amino benzoic acid and diethyl amino ethanol. Hydrolyzed by an esterase in blood.	Hydrolyzed in liver	Probably in liver	Presumably in liver by hydrolysis.
Stability of solutions	Stable May be boiled repeatedly and autoclaved.	Stable May be boiled repeatedly and autoclaved	Stable if boiled for a few minutes.	Stable Sterilized by boiling for 10 min.
Onset of action	Immediate—two to five minutes.	Five to 10 minutes.	Immediat by injection. Two to three minutes topically	Immediate.
Duration	Averages one hour	Averages two hours.	One t two hours.	Three hours.
Dose:				
Intrathecally				
low	50 to 100 mg.	5 to 7½ mgm.	Not used intraspinally	
medium	100 to 150 mg	7½ to 12½ mgm		
high	150 to 200 mg	15 to 20 mgm.		
Peridural	.75 to 1.0 gm. (2%)			Not used intraspinally
Infiltration	1 gm. (1%)	75 mgm. 0.1%.	0.2% solution	Infiltration .25%.
Nerve Block	1 gm (2%.)	75 mg. 0.1%.		Eye 2 to 5%.
Topically	Not effective	2%.		Mucous membranes.
Ointment	Not effective			5 t 10%.
Oil solution	2%			
Remarks	Least toxic and most widely used local anesthetic drug Compatible with epinephrine	Circulatory type of toxic response more common than convulsive reaction. Compatible with epinephrine	Possesses topical activity Little used clinically Compatible with epinephrine	Possesses 2.2 the surface activity of cocaine Compatible with epinephrine No mydriasis.

	Panthesine	Butyn	Monocaine	Benzocaine	Propaesin
Synonyms		Butacaine (U.S.P.)	Butethamine	Anesthesin. Americaine	
Chemical nature	Menthane sulphonat m-diethyl leucinol ester of para amino benzoic acid.	Para amino benzoic acid ester of di-butyl amino propanol.	Para amino benzoic acid ester of mono-isobutyl amino ethanol.	Para amino benzoic acid ester of ethyl alcohol.	Para amino benzoic acid ester of propyl alcohol.
Properties	Hydrochloride White or slightly yellow powder M.P 157 to 158°C. Soluble 1 in 2H_2O. pH 6.0.	Sulphate. White odorless powder Melts 98 to 100°C. Soluble 1 in 1H_2O Soluble in alcohol.	Hydrochloride Soluble white powder with bitter taste Formate more soluble than hydrochloride Used for spinal anesthesia.	Base: white, odorless, tasteless powder One gm. dissolves in 2.5 L H_2O, 5 cc. alcohol, 30 cc almond oil. Soluble in hydrochloric acid.	White odorless, tasteless powder M.P 73°C. Solubility approximately same as benzocaine.
Prepared by	Karrer 1921	Kamm and Volwiler 1918.	Goldberg 1934.		
Potency	Ten times greater than procaine	Surface anesthetic potency approximates cocaine	One and one-half times more potent than procaine	Very low potency due to insolubility in water	Low potency due to insolubility in water
Toxicity	Two to three times greater than procaine	Three times greater than procaine	Approximately as toxic as procaine	Relatively non-toxic due to low water solubility	Relatively non-toxic due to water insolubility
Detoxification	Probably in liver	Probably in liver	Presumably hydrolyzed in liver	Hydrolyzed by liver	Probably by liver.
Stability of solutions	Stable	Stable Solutions sterilized by boiling	Stable May be boiled or autoclaved.	Stable in aqueous alcoholic and oily solutions.	Stable in aqueous and oily solutions and ointments.
Onset of action	Immediate	Immediate.	Immediate	Immediate.	Immediate.
Duration		Approximately one hour	1 to 1½ hours.	As long as it remains in contact.	As long as it remains in contact.
Dose:					
Intrathecally					
low	4 cc 0.5% (20 mgm.)	Not used	40 to 60 mg	Not used.	Not used.
medium		Not used.	60 to 100 mgm.	Not used.	Not used.
high		Not used	100 to 120 mgm.	Not used.	Not used.
Peridural			1%	Not used.	Not used.
Infiltration	0.15 to 2%		½ to 1%	Not used.	Not used.
Nerve Block					
Topically	2%.	2% for eye.			2 to 20% ointment.
Ointment		2% for eye		5% dusting powder	
Oil solution				20% ointment (Americaine)	
Remarks	Not used in clinical practice	Used primarily as topical anesthetic	Offers little more promise than procaine. Has some vasoconstrictor action.	Suitable only as a topical anesthetic. Added to oil solutions for securing prolonged effect.	Suitable only as topical anesthetic.

	Butesin	Orthoform (old)	Orthoform (new)	Locaine	Cocaine
Synonyms			Orthocaine.	PT 19 Peridocaine	
Chemical nature	Para amino benzoic acid ester of propanol.	Methyl ester of 3-hydroxy 4-amino benzoic acid.	Methyl ester of 3-amino 4-hydroxy benzoic acid.	Piperidyl propanol ester of orthoamino benzoic acid.	Benzoic acid ester of methyl ecgonine
Properties	Insoluble white powder melting at 56 to 57°C. Forms yellow salt with picric acid.	White powder Melts at 120–140° Forms hydrochloride Not very soluble in water Salts are more soluble	White odorless, tasteless powder Melts at 141 to 143° Insoluble in water Forms hydrochloride Melts at 190°C. Soluble in water 1 10.	White bitter powder Forms hydrochloride Melts at 200°C. Forms a 2% solution.	Colorless, crystalline, white powder Forms hydrochloride which melts at 183°C. One gram dissolves in 0.4 cc water White powder from coca leaves. Isolated by Gaedicke in 1855
Prepared by					Prepared by Niemann in 1860 Carl Koller in 1884 discovered its value for local anesthesia.
Potency	Parallels benzocaine	Parallels benzocaine.	More potent than benzocaine.	Approximately same as procaine.	Approximately two to three times more potent than procaine.
Toxicity	Low by virtue of poor solubility	Low May be used internally	Low	Approximately same as procaine	Approximately four times more toxic subcutaneously than procaine
Detoxification	Hydrolyzed by liver (?)	Hydrolyzed by liver	In the liver by hydrolysis (?)	Liver?	Approximately 80% hydrolyzed by liver to benzoic acid and ecgonine Rest eliminated unchanged.
Stability of solution	Ointments and solutions stable	Stable.	Stable.	Stable	Not heat stable Decomposed by boiling and upon standing.
Onset of action	Immediate.	Immediate	Immediate	Immediate.	Immediate.
Duration	As long as in contact with tissues.	As long as in contact with tissues.	As long as in contact with tissues.	Averages 45 minutes.	Averages one hour
Dose	Butesin picrate ointment 1%.	Same as orthoform.	Powder with starch 10–20%. Ointment 10–20%.	20 to 40 mgm. for spinal anesthesia.	2 to 4% topically Not recommended for infiltration, nerve block or spinal anesthesia. Is standard of comparison for drugs used topically
Remarks	Used as a surface anesthetic entirely	Same structure as orthoform (new) except position of amino and hydroxyl reversed. Not used clinically	May cause necrosis and inflammation on raw surfaces. Little used clinically	Motor effects minimal. Provides mostly sensory anesthesia.	Possesses mydriatic action, local vasoconstrictor action, addiction properties, generalized vasoconstrictor action. Under Harrison Narcotic Law

	Metycaine	Alypin	Intracaine	Apothesine	Nupercaine
Synonyms	Neothesin. Piperocaine.	Amydricaine	Diethocain. Maxicaine.		Percaine (Brit.) Dibucaine.
Chemical nature	Benzoic acid ester of methyl piperdyl propanol.	Benzoic acid ester of tetra methyl diamine ethyl propanol.	Para ethoxy benzoic acid ester of diethyl amine ethanol.	Cinnamic acid ester of diethyl amino propanol.	Beta diethyl amine ethyl amide of butyloxychinchonic acid.
Properties	White powder Forms hydrochloride. Melts at 172 to 175°C. Soluble 1 in 1 H_2O	White powder Soluble in water and alcohol. Forms hydrochloride which melts at 170°C.	White powder Soluble in water Forms hydrochloride	Hydrochloride is a white powder melting at 136° Soluble in water and alcohol. Free base occurs as an oil.	Hydrochloride is white powder which melts at 97°C. Very soluble in water pH 6 base easily precipitates.
Prepared by	McElvain 1930	1906 by Hoffman.			Meischer 1925
Potency	Approximately 1½ times more potent than procaine	Four to five times more potent than procaine	Approximately 1½ times more potent than procaine	Approximately that of procaine	Approximately 15 times that of procaine.
Toxicity	Slightly greater than procaine	Ten times greater than procaine subcutaneously	Approximately 1½ times that of procaine	Approximately twice as toxic as procaine	Approximately 10 to 15 times greater than procaine.
Detoxification	Hydrolysed in the liver	Hydrolysed in the liver	Hydrolysed in the liver	Hydrolysed in the liver	Hydrolysed in the liver
Stability of solution	Stable May be boiled and autoclaved	Not stable Boiled at 100° Decomposes after 4 to 5 minutes.	Stable Boilable for sterilization.	Stable and boilable.	Stable. May be boiled or autoclaved. Mixes with glucose
Onset of action	Immediat	Immediat	Immediate.	Slower than procaine	Onset in 10 minutes.
Duration	Lasts one hour	Similar to cocaine	Lasts over 1½ hours.	Approximately same as procaine	Lasts 2½ to 3 hours.
Dose Intrathecally low medium high Peridural Infiltration Nerve Block Topically Ointment Oil solution	 50 to 75 mgm 75 to 100 mgm. 100 to 125 mgm. 1%. 1%. 1½%. 2% 4%	Used for topical anesthesia 2 to 4%. Approximates cocaine in potency as topical anesthetic	Approximately ½ dose and concentration of procaine Used for spinal and infiltration. Topical action slight	1½% for infiltration. 2 cc. of a 4% solution for spinal. 2% topical.	Infiltration 0.1%. Block 0.1%. Spinal 2½ to 5 mgm. low 5 to 10 mgm. medium. 10 to 15 mgm. high. 1% ointment. Oil 5 mgm. per cc.
Remarks	Possesses half potency of cocaine topically Does not interfere with action of sulphanilamide	Compatible with epinephrine Not used for injection	Used as substitut for procaine Has little to offer over procaine	Used instead of procaine. Has little to offer over procaine	Not derived from quinine. Most potent local anesthetic. Possesses some local toxicity Causes slough when injected subcutaneously

	Eucupine	Quinine	Phenacaine	Bromsalizol	Benzyl Alcohol	Xylocaine
Synonyms			Holocaine			Lidocaine
Chemical nature	An alkaloid-isoamyl hydrocupreine. Related to quinine	An alkaloid-methyl cupreine. Contains 2 nitrogen atoms. Highly basic	Not an ester. Built from phenetidin molecule.	3-Monobrom 2-hydroxy benzyl alcohol.	Phenyl carbinol, an aromatic alcohol.	ω diethylamino 2,6-dimethyl acet amide
Properties	Forms dihydrochloride. Has two nitrogen atoms. White powder soluble 1 in 1 H_2O at 15°C.	White, bitter powder forming salts with acids. Hydrochloride combined with urea most soluble preparation used for anesthesia.	Forms a hydrochloride-white powder. Melts at 190° Soluble 1 in 50 H_2O, also alcohol (U.S.P.)	White powder M.P. 107 to 109°C. Forms 1% solution in water. Soluble in alcohol, ether oils, and glycol.	Colorless liquid with faint aromatic odor. Soluble 1 in 25 water. Boils at 205°C. Freely soluble in alcohol, ether, etc.	Base forms hydrochloride which is white powder stable and sterilizable.
Prepared by	Synthesized from quinine.	From cinchona bark.		Described by Macht and Dunning.	Found in Jasmin and Peru and Tolu balsams.	Lofgren and Lundquist in 1943.
Potency	25 times more potent than cocaine topically. Ten to twenty times more than procaine subcutaneously	Considerably greater than procaine.	Potency same as cocaine for topical use.	Low potency similar to benzocaine.	Low potency similar to benzocaine.	Approximately twice as potent and toxic as procaine. Possesses topical action.
Toxicity	Locally toxic. Low systemic toxicity. Twice that of quinine	Locally toxic. Produces slough. Excitation characteristic of procaine does not follow intravenous use.	Subcutaneous toxicity twice that of cocaine. I.V. equals cocaine.	Non-toxic. Used orally as an antispasmodic. No convulsions intravenously	Non-toxic. May be taken orally to relieve spasm.	Same systemic effects as procaine. Tends to produce drowsiness and amnesia. Rapid absorption causes convulsion.
Detoxification	Detoxified in liver. All of an I.V. dose eliminated in 24 hrs.	Liver	Destroyed in liver and eliminated slowly	Liver?	Liver?	Liver slowly hydrolized.
Stability of solution	Stable in oil and water. Germicidal, boilable and can be autoclaved.	Stable in oil and water solution	Stable	Boilable. Self-sterilizing.	Boilable and stable.	Stable and boilable. Not an ester I an amide.
Onset of action	Slow. Causes burning.	Slow onset	Similar to cocaine.	Slowly	In several minutes.	Immediate. Diffuses rapidly into tissues.
Duration	Several hours. Oil solution 10 hours to weeks.	Several days to weeks.	Similar to cocaine.	10 days to weeks.	Many hours when used in combination with procaine.	1-1½ hours without epinephrine when infiltrated. 2 hours with epinephrine
Dose	Spinal—not used. Infiltration 0.1%. Topical 0.5 to 1%. 2.5% in oil 1-3 cc. at each injection site. Open wound 0.5 to 1.0%.	Rarely used. 6% causes slough at injection site	1% for topical use in eye	½% infiltration. 4% in peanut oil. 20% in propylene glycol.	1 to 4% topically or infiltration. Not recommended for infiltration.	½ to 2% solution for infiltration up to 4% topically. Maximum ½ gram.
Remarks	May cause slough. Used in combination with procaine to obtain prompt anesthesia.	Causes slough. Precipitates in tissues. Poorly soluble.	Action preceded by smarting and erythema.	No salt forms due to OH, but OH needed for activity. Some local tissue irritation occurs.	Local irritation. Usually combined with procaine benzocaine, etc. for prolonged use.	Not irritating to tissues.

	Metycaine	Alypin	Intracaine	Apothesine	Nupercaine
Synonyms	Neothesin. Piperocaine.	Amydricaine	Diethocain. Mardesine.		Percaine (Brit.) Dibucaine
Chemical nature	Benzoic acid ester of methyl piperdyl propanol.	Benzoic acid ester of tetra methyl diamine ethyl propanol.	Para ethoxy benzoic acid ester of diethyl amino ethanol.	Cinnamic acid ester of diethyl amino propanol	Beta diethyl amino ethyl amide of butyloxycinchonic acid.
Properties	White powder Forms hydrochloride Melts at 172 to 175°C. Soluble 1 in 1 H_2O	White powder Soluble in water and alcohol. Forms hydrochloride which melts at 170°C.	Whit powder Soluble in water Forms hydrochloride	Hydrochloride is a white powder melting at 136° Soluble in water and alcohol. Free base occurs as an oil.	Hydrochloride is white powder which melts at 97°C. Very soluble in water pH 6 base easily precipitates.
Prepared by	McElvain 1930.	1906 by Hoffman.			Meischer 1929.
Potency	Approximately 1½ times more potent than procaine.	Four to five times more potent than procaine	Approximately 1½ times more potent than procaine	Approximately that of procaine	Approximately 15 times that of procaine
Toxicity	Slightly greater than procaine	Ten times greater than procaine subcutaneously	Approximately 1½ times that of procaine.	Approximately twice as toxic as procaine	Approximately 10 to 15 times greater than procaine.
Detoxification	Hydrolyzed in the liver	Hydrolyzed in the liver	Hydrolyzed in the liver	Hydrolyzed in the liver	Hydrolyzed in the liver
Stability of solution	Stable. May be boiled and autoclaved	Not stable Boiled t 100° Decomposes after 4 to 5 minutes.	Stable Boilable for sterilization.	Stable and boilable.	Stable May be boiled or autoclaved. Mixes with glucose
Onset of action	Immediat	Immediate	Immediate.	Slower than procaine.	Onset in 10 minutes
Duration	Lasts one hour	Similar t cocaine.	Lasts over 1½ hours.	Approximately same as procaine	Lasts 2½ to 3 hours.
Dose Intrathecally low medium high Peridural Infiltration Nerve Block Topically Ointment Oil solution	 50 to 75 mgm 75 to 100 mgm. 100 to 125 mgm. 1%. 1%. 1½%. 5%. 4%.	Used for topical anesthesia 2 to 4%. Approximates cocaine in potency as topical anesthetic	Approximately ⅔ dose and concentration of procaine Used for spinal and infiltration Topical action slight.	1½% for infiltration 2 cc of 4% solution for spinal. 2% topical	Infiltration 0.1%. Block 0.1%. Spinal. 2½ to 5 mgm. low 5 to 10 mgm. medium, 10 to 15 mgm. high. 1% ointment. Oil 5 mgm. per cc.
Remarks	Possesses half potency of cocaine topically Does not interfere with action of sulphanilamide	Compatible with epinephrine Not used for injection.	Used as substitute for procaine Has little to offer over procaine	Used instead of procaine. Has little to offer over procaine	Not derived from quinine Most potent local anesthetic. Possesses some local toxicity Causes slough when injected subcutaneously

	Eucupine	Quinine	Phenacaine	Bromsalizol	Benzyl Alcohol	Xylocaine
Synonyms			Holocaine.			Lidocaine
Chemical nature	An alkaloid-isoamyl hydrocupreine. Related to quinine	An alkaloid-methyl cupreine. Contains two nitrogen atoms. Highly basic	Not an ester. Built from phenetidin molecule.	5-Monobrom 2-hydroxy benzyl alcohol.	Phenyl carbinol, an aromatic alcohol.	ω diethylamino. 2,6-dimethyl acet amide.
Properties	Forms a dihydrochloride. Has two nitrogen atoms. White powder soluble 1 in $1H_2O$ at 15°C.	White, bitter powder forming salts with acids. Hydrochloride combined with urea most soluble preparation used for anesthesia.	Forms hydrochloride-white powder. Melts at 190° Soluble 1 in 50 H_2O, also alcohol (U.S.P.)	White powder M.P. 107 to 108°C. Forms 1% solution in water. Soluble in alcohol, ether oils, and glycol.	Colorless liquid with faint aromatic odor. Soluble 1 in 25 water. Boils at 205°C. Freely soluble in alcohol, ether etc.	Base forms hydrochloride which is white powder stable and sterilizable.
Prepared by	Synthesized from quinine.	From cinchona bark.		Described by Macht and Dunning	Found in Jasmin and Peru and Tolu balsams.	Lofgren and Lundquist in 1943.
Potency	25 times more potent than cocaine topically. Ten to twenty times more than procaine subcutaneously	Considerably greater than procaine.	Potency same as cocaine for topical use.	Low potency similar to benzocaine.	Low potency similar to benzocaine.	Approximately twice as potent and toxic as procaine. Possesses topical action.
Toxicity	Locally toxic. Low systemic toxicity. Twice that of quinine	Locally toxic. Produces slough. Excitation characteristic of procaine does not follow intravenous use.	Subcutaneous toxicity twice that of cocaine. I.V. equals cocaine.	Non-toxic. Used orally as an antispasmodic. No convulsions intravenously	Non-toxic. May be taken orally to relieve spasm.	Same systemic effects as procaine. Tends to produce drowsiness and amnesia. Rapid absorption causes convulsion.
Detoxification	Detoxified in liver. All of an I.V. dose eliminated in 24 hrs.	Liver	Destroyed in liver and eliminated slowly	Liver?	Liver?	Liver slowly hydrolized.
Stability of solution	Stable in oil and water. Germicidal, boilable and can be autoclaved.	Stable in oil and water solution.	Stable	Boilable. Self-sterilizing.	Boilable and stable.	Stable and boilable. Not an ester. Is an amide
Onset of action	Slow. Causes burning.	Slow onset.	Similar to cocaine.	Slowly	In several minutes.	Immediate. Diffuses rapidly into tissue.
Duration	Several hours. Oil solution 10 hours to weeks	Several days to weeks	Similar to cocaine.	10 days to weeks.	Many hours when used in combination with procaine.	1–1½ hours without epinephrine when infiltrated. 2 hours with epinephrine
Dose	Spinal—not used. Infiltration 0.1%. Topical 0.5 to 1%. 0.5% in oil 1–6 cc at each injection site. Open wound 0.5 to 1.0%.	Rarely used. 6% causes slough at injection site	1% for topical use in eye.	1% infiltration. 4% in peanut oil. 20% in propylene glycol.	1 to 4% topically or infiltration. Not recommended for infiltration.	½ to 2% solution for infiltration up to 4% topically. Maximum ½ gram.
Remarks	May cause slough. Used in combination with procaine to obtain prompt anesthesia.	Causes slough. Precipitates in tissues. Poorly soluble.	Action preceded by smarting and erythema.	No salt forms due to OH, but OH needed for activity. Some local tissue irritation occurs.	Local irritation. Usually combined with procaine benzocaine, etc. for prolonged use.	Not irritating to tissues.

Name	Amolanone	Benoxinate	Chloroprocaine	Hydroxyprocaine
Synonym	Amethone	Dorsacaine, Butoxyprocaine	Nesacaine	Oxyprocaine
Chemical structure	3 (beta diethyl amino ethyl 3, phenyl 2,benzo-furanone	3n butoxy diethyl amino ethanol ester of p,amino benzoic acid	Diethyl amino ester of 2, chlor 4, aminobenzoic acid	OH in position 2 in procaine
Properties	Topical anesthetic, anticholinergic	White, odorless crystalline powder butoxy benzoic acid.	White powder soluble in water	Similar to procaine.
Potency	Low potency	Similar to tetracaine.	Similar to procaine.	Similar to procaine. Onset more rapid, duration slightly longer
Toxicity	Used I.M. as spasmolytic. Not a convulsant.	Similar to tetracaine.	More rapidly hydrolyzed than procaine.	Slightly more toxic than procaine.
Detoxification		By hydrolysis.	By hydrolysis, aided by liver and plasma esterases.	By hydrolysis.
Stability	Hydrochloride salt is stable.	Forms stable salts with hydrochloric acid.	Stable.	Similar to procaine
Onset of action	5 minutes	Similar to tetracaine	Similar to procaine.	More rapid than with procaine.
Dose	As .25% solution topically	0.4% solution 1 or 2 drops in each eye.	Similar to procaine. Uses same as for procaine.	Similar to procaine.
Remarks	Possesses spasmolytic action used I.M. Not used for injection. Used for topical anesthesia in lower urinary tract.	A para-amino benzoic acid ester. Similar to procaine, except that a C_4H_9O group is in position 3 of aromatic nucleus. Used for topical anesthesia of eye. Differs from symprocaine (WIN 3706) which has butoxy in position 2.	No effect topically. Systemic reactions less frequent than procaine. Structure same as procaine except a Cl appears in position 2 on aromatic nucleus.	Possesses bacteriostatic properties. Same as procaine except an OH appears on position 2 of aromatic nucleus.

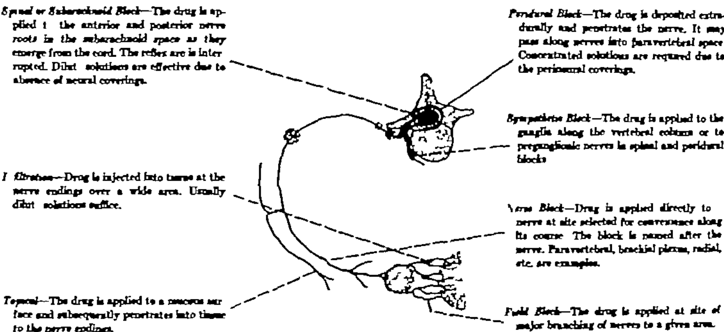
Name	Metahydroxy procaine	Carbocaine	Ravocaine	Hydroxytetracaine
Synonym		WIN 9135	Propoxycaine Pravocaine	Rhenocaine
Chemical structure	3, hydroxy procaine	dl N-methyl-pipecolic acid 2,6, dimethyl anilide.	Same as procaine, except that a propoxy group is on position 2	OH in position 2 of tetracaine
Properties	Used as the sodium salt.	Similar to lidocaine. Forms a hydrochloride	Stable, white powder M.P 146°C. Forms a 20% solution in water	Forms a hydrochloride
Potency	Slightly more than procaine	Twice that of procaine, somewhat greater than lidocaine	Surface action twice as potent as cocaine. Similar to tetracaine for injection.	Less than tetracaine
Toxicity	Slightly less than procaine	Approximately twice that of procaine but less than lidocaine	Twice as toxic as tetracaine.	One-third as toxic as tetracaine.
Detoxification	Presumably similar to procaine	Slowly hydrolyzed.	By hydrolysis in liver and plasma.	Presumably by hydrolysis
Stability	Similar to procaine	Chemically allied to lidocaine An amide and not an ester	Boilable, stable. Used as hydrochloride pH—4.6	Less stable than tetracaine
Onset of action	Similar to procain	Similar to procaine. Duration similar to lidocaine.	Similar to procaine. Diffuses rapidly through tissues.	Used for topical anesthesia.
Dose	Similar to procaine.	1½, 1 and 2% solution.	0.1% infiltration.	
Remarks	Same as OH in position 3 on aromatic nucleus of procaine.	Used for infiltration and nerve block. Possesses some vasoconstrictor activity	Inactivated by glucose. Inositol used instead. Compatible with epinephrine.	

Name	*Dyclonine*	*Pramoxine*	*Naepaine*	*Dimethisoquin*
Synonym	Dyclone, Falicaine	Tronothane	Amylsine	Quotane
Chemical structure	4, butoxy 3, piperidine propiophenone	4(3-p butoxy phenoxy propyl) morpholine hydrochloride	2, amylamino ethyl para-amino benzoate hydrochloride	3, butyl 1, dimethyl amino ethoxy isoquinoline hydrochloride.
Properties	White powder soluble in water Forms hydrochloride.	White powder soluble in water	White crystalline bitter powder Soluble in water and alcohol.	White powder Bitter numbing taste and aromatic odor Stable in alcohol and water.
Potency	Similar to cocaine topically	Low potency Similar to benzocaine.	Similar to cocaine.	Less than dibucaine, greater than cocaine.
Toxicity	Low human toxicity Oral or I V doses cause no circulatory respiratory effects. Not convulsant.	Low toxicity Sensitizing potential low	Convulsant, similar to cocaine.	Not established. Greater than cocaine. Not used except on skin.
Detoxification	Not altered in body	Not established.	Presumably by hydrolysis.	Presumably by hydrolysis.
Stability	Hydrochloride salt stabilized with chlorbutanol. *Heat labile.* Not to be boiled.	Hydrochloride salt stable in *air pH of solution is acid.*	Hydrochloride salt stable in air pH—[illegible].	Hydrochloride salt stable in air pH-[illegible].
Onset of action	Topically only Long latent period, 5–10 minutes. Long duration once anesthesia established.	*3–5 minutes*	Within several minutes with smarting.	*Few minutes,* lasts 2–4 hours.
Dose	*1% ointment or ½–1% solution* topically	*For anesthesia on skin or rec*tum (1% ointment)	*2–4% solution 1–2 drops in eye.*	0.5% lotion or ointment on skin.
Remarks	To be used topically only Not for injection. Concentrations greater than 1% cause necrosis. Has been used I.V 0 1% solution in amounts up to 5–10 cc. *Bacteriostatic. Self-sterilizing.* Does not have amide or ester type linkage. Included in N.N.R.	Not for ocular, nasal or oral use or for injection. Included in N.N.R. Not an ester or amide.	Does not cause miosis or increase intra-ocular tension. A derivative of para-amino benzoic acid. Included in N.N.R.	Used on skin. Not recommended for injection or on mucous membranes. Included in N.N.R.

Name	Meprylcaine	Kincaine	Metabutethamine	Primacaine
Synonym	Oracaine			
Chemical structure	2, methyl 2, propanyl amino benzoate	2, isobutyl 2, methyl propanyl benzoate.	2, isobutyl amino ethyl meta amino benzoate.	diethyl amino 2, butoxy 3, amino benzoate.
Preparation	White powder M.P. 151°C. Hydrochloride salt.	White powder	Whit powder Melts at 192°C. Hydrochloride salt.	White powder Melts at 118°C. pH-4.2
Potency	Similar to procaine		Twice that of procaine.	Four times more potent than procaine.
Toxicity	Less tha procaine.		2 3 times that of procaine.	About twice that of procaine.
Detoxification	Hydrolyzed rapidly in liver	Presumably by hydrolysis.	By hydrolysis in plasma and liver	By hydrolysis.
Stability	Hydrochloride is a white powder		Hydrochloride solutions not stable.	Very soluble. Forms a 75% solution.
Onset of action	More rapid than procaine. Duration similar to procaine.		Rapid like procaine.	Immediate. Lasts 1 1½ hours.
Dose	2% solution for infiltration. Maximum 20 cc.		3.8% solution. Used in dentistry 20 cc. maximum.	1.5% solution 20 cc. maximum.
Remarks	Used largely in dentistry	Used in dentistry	More toxic than procaine. A meta amino benzoate.	A meta amino benzoic acid derivative.

REGIONAL ANESTHESIA

Regional anesthesia, also known as conduction anesthesia, is accomplished by applying a local anesthetic drug to a nerve cell or fibre or ganglion and blocking efferent and afferent conduction from the site of application of the drug. *Regional anesthesia is classified according to site of application of drug as follows*



PHYSIOLOGY OF REGIONAL ANESTHESIA

Effect of Electrolytes of Tissues—Buffering action nullifies any effects of acidification or alkalinization. Solution tends to approach pH of tissues.

Effect of Drug on Nerve Fibres
(a) Sensory. Usually affected first. Are smallest.
(b) Autonomic usually after sensory fibres. Smaller fibre before larger.
(c) *Motor. Are largest. Usually last to be affected.*

Effect of Vasoconstrictors—Retard absorption of drug and prolong anesthesia. Also reduce toxicity

Effect on Tissues—Hypertonic or hypotonic solutions cause edema and post anesthetic soreness.

Effect of Heat—Warming solution increases onset of anesthesia.

Effect on Blood Vessels—Dilated due to autonomic blockade unless vasoconstrictors are added or cocaine is used.

PHYSIOLOGY OF SPINAL ANESTHESIA

Cortex—Not affected. Depressed if blood pressure falls to shock levels. Consciousness may be lost.

Respiratory Center—Depressed during hypotension. Apnea results from ensuing cerebral anemia.

Vasomotor Center—Active. Control of vessels in anesthetized area lost.

Vagus Center—*Remains active.* Vagal tone predominates in segments where sympathetic activity is abolished.

Cough Center—Remains active

Vomiting Center—Ordinarily not affected. May be excited by:
(1) Afferent impulses along vagi due to traction on abdominal viscera.
(2) Cerebral anemia secondary to hypotension.
(3) Stimulation by drug which diffuses into cisterna.

Carotid-aortic Bodies—Not affected

Carotid Sinus—Depressed if level extends to D4

Lungs—Slight increase in respiratory rate. Intercostal muscles paralyzed in "high spinal." Not affected in "low spinal." Paresis at intermediate level. Minute volume exchange may decrease. Decreases in "high spinal." No effect on alveoli. Bronchi may constrict in "high spinal" due to predominance of vagal activity.

Metabolism—Decreased due to decreased muscle activity.

Diaphragm—Increased activity to compensate for intercostal paralysis in "high spinal." Diaphragmatic activity returns before intercostal activity in total spinal block.

Adrenal—Epinephrine content depleted. Not the cause of hypotension.

Liver—No significant change in function unless severe hypotension follows and remains untreated.

Bile—Unchanged

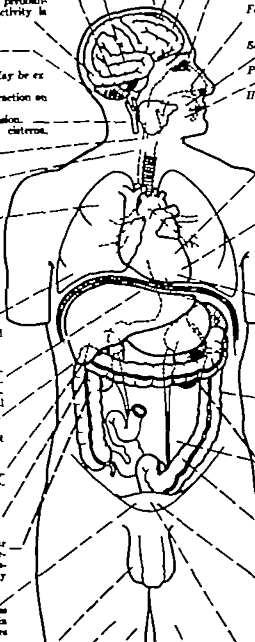
Kidney—No change effect upon glomerular filtration, tubular reabsorption, or secretion. Urine continues to form during anesthesia. Overdistension of bladder may result during surgery.

Bladder—Atony during and loss of stimulus to void often leads to retention of urine in postoperative period. Cystometric studies reveal increase in bladder capacity.

Sphincters—Relaxed.

Skeletal Muscles—Complete relaxation in anesthetized area. Leg volume increased due to relaxation and pooling of blood in vessels.

Body Temperature—Decreased from loss of control of heat regulating center, decreased muscle activity and cutaneous vasodilatation.



Intracranial Pressure—Not affected. Increased during straining. Post lumbar puncture headache frequent. Cause not known.

Eyes—Not affected. Diplopia may result from paralysis of 4th or 6th nerve postoperatively.

Cranial Nerves—Not affected. Palsies may occur postoperatively. Cause not known.

Face—Pallor due to vasoconstriction. Sweating in unanesthetized area.

Salivary Gland—Not affected.

Pharynx and larynx—Not affected

Heart—Myocardium and conduction tissue not affected. Bradycardia prominent. Cardiac output decreased 10% or more. Stroke volume decreased. Circulation time prolonged 100%. Cardio-accelerator nerves depressed. Vagi remain active.

Blood Pressure—Systolic falls; diastolic falls slightly or is sustained at or slightly below pre-anesthetic level. Decreased cardiac output and decreased stroke volume from failure of venous circulation. Renal and splanchnic arterioles under autonomous control do not dilate; peripheral arterioles under sympathetic control do dilate. More pronounced fall in high spinal anesthesia and hyper- and hypotension. Pulse pressure markedly reduced.

Venous Return—Decreased due to relaxation of muscles in the extremities, reduced negative pressure from decreased thoracic movements and change in intra-abdominal pressure.

Gastrointestinal System—Bowel constricted. Increased tone and peristalsis due to parasympathetic predominance when sympathetic activity is abolished.

Pancreas—No effect on secretion or blood amylase or other pancreatic function.

Spleen—Increased in size two or three times if of normal structure.

Lymphatics—No increase in absorption of "toxic" substances from peritoneal cavity if peritonitis is present.

Uterus—No loss of uterine tone or motility. Pain of contractions released by blocking segments below D10. Contractions inhibited above D10.

Fetus—No effect on fetus. Breath spontaneously without resuscitation in uncomplicated obstetrics.

Skin—Vessels dilated from loss of sympathetic activity. Temperature rise as much as 10°F. Absence of sweating in anesthetized area. Marked pallor in unanesthetized portion.

Blood Volume—Not significantly altered. Disparity between blood volume and vascular space occurs from vasodilatation. Corrected by administration of vasoconstrictors rather than fluids.

Non-protein Nitrogen—Unchanged.

Oxygen Capacity—Unchanged if circulatory depression is overcome.

Serum Protein—Unchanged.

Oxygen Content—Slightly increased in arterial blood. Decreased in venous blood. Widened A V difference may cause tissue anoxia.

Urea—Unchanged.

Red Blood Cells—No change or slight increase

Blood Glucose—Not affected. May increase if hypotension remains uncorrected or vasoconstrictors are used.

Leukocytes—Polymorphonuclear cells increase during first twenty-four hours in post-anesthetic period.

Bleeding Time—Unchanged.

Carbon Dioxide Content—Unchanged if respiration is not depressed.

Carbon Dioxide Combining Power—Not affected.

Clotting Time—Unchanged.

USES

1. For operations requiring extreme degrees of muscle relaxation.
2. For operations in which general anesthesia is contraindicated.

CONTRAINDICATIONS

1. The presence of cardiac disease of all types, particularly coronary insufficiency or decompensation, or myocardial disease.
2. The presence of hypotension from any cause
3. The presence of severe hypertension.
4. The presence of disease (infectious or otherwise) of the central nervous system.
5. The presence of anemia from any cause
6. The presence of states accompanied by decreased blood volume
7. The presence of septicemia or infections about the vertebral column.
8. The presence of diseases characterized by marked increases in intra abdominal pressure
9. In psychically disturbed or apprehensive and uncooperative subjects.
10. The presence of diseases accompanied by reduction in pulmonary ventilation.

ADVANTAGES

1. It provides excellent muscle relaxation.
2. It causes no significant blood chemical changes.
3. Suitable where basal narcotics and inhalation anesthetics are contraindicated
4. It allows use of cautery and electrical appliances during surgery
5. It is inexpensive in comparison to other forms of anesthesia.

DISADVANTAGES

1. It is non-controllable. Once it has been administered it cannot be withdrawn.
2. Possibility of failure cannot be wholly excluded.
3. Not safe for surgery above the diaphragm.
4. Distressing circulatory disturbances are common.
5. Post-operative headaches frequent.
6. Psychically unsuited for apprehensive patients.
7. Vagal pathways not blocked in abdominal surgery allowing undesirable reflex stimulation.
8. May be followed by various neurological complications, many of which are serious and permanent (myelitis, etc.).

NEUROLOGICAL COMPLICATIONS OF SPINAL ANESTHESIA

Headache—Usually occurs after first day. Is usually intermittent, throbbing and aggravated by changes in posture. May last several days to months. Responds to analgesics, intrathecal injection of saline or peridural injection of saline. Believed to be due to leakage of cerebrospinal fluid from site of puncture.

Cranial Nerves—Palsies transient in nature of IV, VI, VII and various components of spinal nerve, occur after first 24 hours. May last up to 6 to 10 weeks. Not necessarily found in areas anesthetized by drug. Most often involves VI cranial.

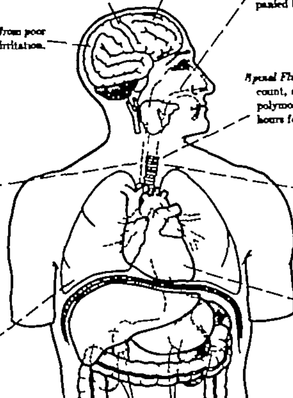
Cord—Myelitis uncommon. Usually extends into cauda equina and causes permanent paralysis of the lower extremities. Is the most serious complication. Often associated with diseases of the spinal cord. Accompanied by fecal and urinary incontinence.

Meninges—*Meningitis follows contamination from poor* technique or inflammation due to chemical irritation.

Spinal Fluid—Little or no significant change in cellular count, sugar or colloidal gold. Transient increase in polymorphonuclear cells and glucose during first 18 hours followed by a return to normal.

Meningismus—Usually occurs early. Believed to be due to chemical irritation. Difficult to differentiate from meningitis.

Cells—Toxic doses cause chromatolysis, dissolution of Nissl substance, swelling of cell membrane with recovery after 90 days.



Circulatory System—Circulatory failure of neurogenic origin follows blockade. Severe hypotension not infrequent. Respiratory failure may follow due to cerebral anemia.

Respiratory System—Respiratory failure follows when drug ascends into thoracic and cervical segments, paralyzing intercostal muscles and diaphragm.

INTRINSIC FACTORS INFLUENCING LEVEL OF SPINAL ANESTHESIA

1. *Diameter of Spinal Cord*—Fairly constant. Has little effect.
2. *Subarachnoid Volume*—Fairly constant. Has little effect.
3. *Length of Spinal Cord*—Varies. Dosage should be in proportion to number of segments to be anesthetized.

EXTRINSIC FACTORS INFLUENCING LEVEL OF SPINAL ANESTHESIA

1. *Rate of Injection*—The faster the rate, the higher the ascent.
2. *Volume of Solution*—The greater the volume the greater the spread of solution to spinal segments.
3. *Concentration*—The greater the total dose the greater the number of segments involved and the greater the intensity of anesthesia.
4. *Site of Injection*—Must be low for distribution involving only lumbar or sacral segments.
5. *Specific Gravity of Solution*—Hyperbaric solutions gravitate downward, hypobaric upward, isobaric variable.
6. *Position of Patient*—Hyperbaric solutions migrate cephalad. Hypobaric solution caudad in head-down position.

FACTORS INFLUENCING DURATION OF SPINAL ANESTHESIA

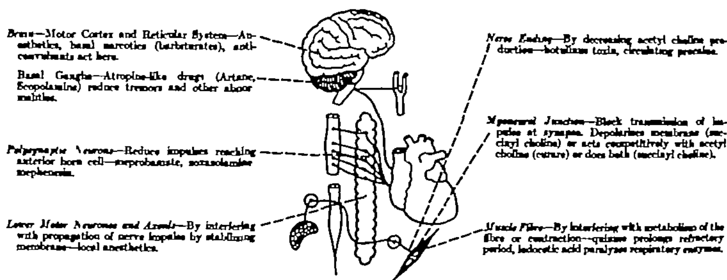
1. *Chemical Nature of Drug*—Most important factor. Onset delayed with longer-lasting drugs.
2. *Dose of Drug*—Not important. Influences number of dermatomes involved. Duration increases up to given point as dose increases beyond which increase in dose is ineffective.
3. *Response of Tissue to Drug*—Intensity and duration vary with individuals.
4. *Presence of Vasoconstrictors*—Epinephrine added to agent prolongs duration up to 60%. Pitressin and nor-epinephrine equally as effective. Ephedrine not effective.

SECTION XII NON ANESTHETIC DRUGS USED IN CONJUNCTION WITH ANESTHESIA

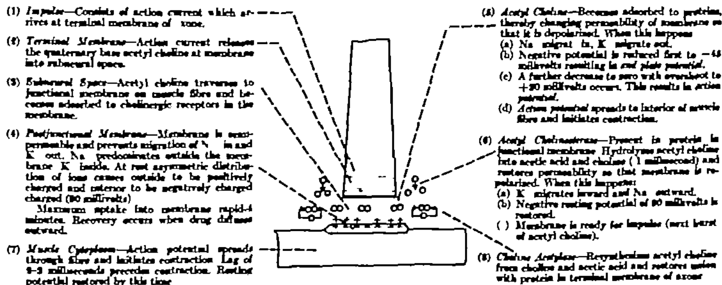
SKELETAL MUSCLE RELAXANTS

POSSIBLE SITES OF ACTION ON MOTOR SYSTEM

Muscle tone may be decreased by drugs acting at the following sites



MECHANISM OF NEUROMUSCULAR TRANSMISSION



MECHANISM OF ACTION OF NEUROMUSCULAR BLOCKING AGENTS

Mechanism of Neuromuscular Block—Neuromuscular transmission is inhibited by: (1) anti-depolarizing drugs. These are preferentially bound to cholinergic receptors. They do not possess the action of acetyl choline but prevent acetyl choline from depolarizing. They act by competitive inhibition. (2) Depolarizing drugs. These are quaternary bases which act similarly to acetyl choline but for longer time thereby causing persistent depolarization which produces contraction followed by the flaccidity. (3) Drugs causing dual block. Membrane first becomes depolarized but the drug penetrates into fibre and acts as non-depolarizer even though the membrane potential is restored. Also known as biphasic block.

PHYSIOLOGICAL ALTERATIONS AT END PLATE CAUSED BY ANTI-DEPOLARIZERS (NON DEPOLARIZERS)

Acetyl Choline—Continues to form and be hydrolysed without interference by relaxant.

Acetyl Cholinesterase—Continues t act uninhibited by relaxant.

Membrane Potential—Remains unchanged. Electrical activity unchanged.

Cytoplasm—Not altered. Muscle fibre responds to electrical stimuli.

Anti-Cholinesterase—Permits acetyl choline to accumulate and overcome block. Large doses inhibit. Excess acetyl choline accumulates which may enhance blockade by causing persistent depolarization.

Membrane—Non-depolarizers have broad molecules and do not penetrate into fibre (pachycurare) Membrane not depolarized.

Blood Flow of End Plate—Increases in blood flow accelerate rate of recovery. Cold reduces flow—Increases duration of block.

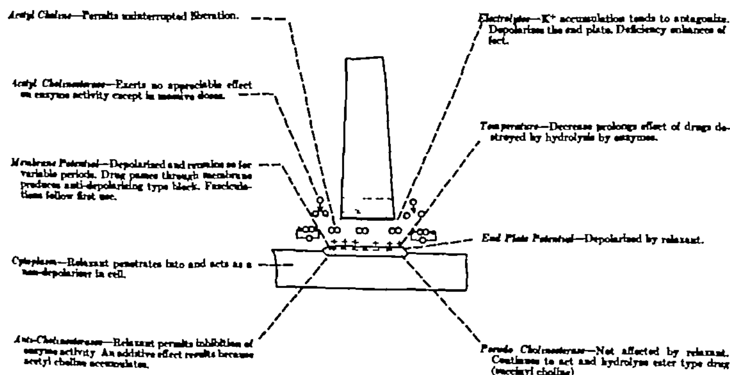
Electrolytes—K^+ antagonizes block. Dehydration enhances effects by causing ionic imbalance (deficiency of K.)

Temperature—Cold causes contraction of blood vessels, reduces blood supply and prolongs block.

Recovery—Maximal when drug is removed.

Antagonists—Edrophonium (Tensilon) antagonizes anti-depolarizers. Acts (1) by protecting acetyl choline from hydrolysis and allowing it t accumulate, (2) by combining with relaxant and removing it from sphere of action, and (3) by acting like acetyl choline and depolarizing membrane.

PHYSIOLOGICAL ALTERATIONS AT END PLATE CAUSED BY DEPOLARIZING BLOCKING AGENTS



CHEMISTRY OF NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents are quaternary bases (R_4NOH) derived from nitrogen. Few are tertiary amines (erythroidine alkaloids). Other pentavalent elements (arsenic, phosphorus, bismuth) may form bases which act qualitatively similarly. Group is called "onium" group. Blockade probably due to the positively charged ion. Mono and tri-quaternary bases (Gallamine) may have curaremimetic activity but they are in the minority. The majority are di or bis-quaternary bases. They have two nitrogen atoms with valence of 5 and the following characteristics

(1) Nitrogen atoms are approximately 14 Å (10 carbon atoms) apart.
(2) They form salts with acids (hydrochloric, hydroiodic and hydrobromic)
(3) Straight chain compounds are usually referred to as "methonium" derivatives.
(4) They are allied to ammonium hydroxide. The hydrogen atoms are replaced by methyl groups.
(5) Cyclic structures whose combined length when placed in succession maintain the nitrogen atoms the conventional distance of 14 Å
(6) Two types of molecules—slender and broad. Slender molecules (leptocurares) penetrate the myoneural junction while broad (pachycurares) do not.
(7) They ionize and yield a positively charged cation and anion. The cation causes the relaxation and forms an ionic bond with the cholinergic receptors.
(8) Methyl substitutions of the nitrogen atom confer greater neuromuscular blocking action than ethyl. Ethyl substituted compounds show greater ganglionic blocking effect.
(9) Quaternary bases penetrate blood brain and epithelial barriers poorly. Absorption is poor. They pass through the glomerular membrane.
(10) They are eliminated unchanged or detoxified slowly by the liver

DISTRIBUTION IN TISSUES

Rate of curarization and recovery are dependent upon the ability of the drug to diffuse in and out of the receptor substance. After an intravenous administration

(1) The highest plasma concentration is attained shortly after termination of the injection.
(2) Paralysis develops when the concentration necessary to produce block penetrates the end plate membrane.
(3) Uptake at end plate is preferential to other tissues and occurs quickly
(4) The peak concentration at the end plate is attained in relatively brief time interval compared to peak in other tissues (3 or 4 minutes versus 1 hour) for tubocurarine.
(5) Little of the relaxant is decomposed or excreted while block is in progress.
(6) The neuromuscular block is terminated after re-entry of drug from end plate to plasma.

Degree of blockade varies with.

(1) Mode of administration. I.V. yields response more rapid and more intense than I.M.
(2) Distribution, excretion and metabolism of the drug.
(3) Body temperature (cold reduces blood supply or enzyme activity)
(4) Electrolyte imbalance and state of hydration (K deficiency enhances effect)

Uses of Muscle Relaxants

1. As an adjunct to anesthesia to obtain muscle relaxation.
2. To "soften" convulsions during electroshock therapy
3. To deliberately produce apnea when indicated in resuscitation (Iron Lung, chest surgery, etc.)
4. To relieve laryngeal spasm.
5. To relieve spasms in disease states (tetanus, rabies)

Advantages of Relaxants

1. Allows use of lighter planes of anesthesia or use of impotent agents (N_2O).
2. Have no central depressant effect.
3. No after-effects (nausea)

Disadvantages

1. Causes hypoventilation along with surgical relaxation.
2. Repeated doses required, cumulative effects result.
3. Influenced by disturbances in electrolyte balance.
4. *Prolonged apnea of obscure etiology encountered.*
5. Muscular pains postoperatively (depolarizing type)
6. Complete muscle activity not fully recovered for many hours after apparent return of tone.
7. Antagonists either not available or not fully reliable.

COMPLICATIONS USING MUSCLE RELAXANTS

A. VASCULAR

1. Hypotension
   (a) From ganglionic blockade using excessive doses of relaxant itself.
   (b) From histamine release.
   (c) From decreased venous return from (1) pooling of blood in the relaxed muscle, (2) decreased thoracic and abdominal excursions or (3) positive pressure on airway (controlled respiration)
   (d) From vagolytic action—tachycardia with decreased cardiac output (Gallamine)
   (e) Overdosage of antagonists causing preganglionic blockade.
2. Bradycardia and Cardiac Arrest
   ( ) Use of parasympathomimetic antagonists (neostigmine) without preliminary use of atropine.
   (b) Use of benzoquinonium (bradycardia from vagal action)
3. Tachycardia
   ( ) Vagolytic action (Gallamine).
   (b) Anti-cholinergic drug mixed with antagonist or with premedication.
4. Hypertension
   (a) Relative inhibition of cardiac vagus giving tachycardia and elevation in blood pressure.
   (b) Inadequate ventilation causing hypercarbia.
   (c) Ganglionic stimulation of weak agents.

B RESPIRATORY

1. Hypoventilation, Apnea
   ( ) Overdosage of drug causing sustained peripheral effect.
   (b) Delayed excretion (renal and liver disease).
   (c) Electrolyte imbalance (dehydration causing hypokalemia).
   (d) Potentiation by anesthetics (ether) antibiotics (neostigmine).
   ( ) Muscular diseases (myasthenia gravis).
   (f) Decreased serum cholinesterase (using succinyl choline)
      (1) in liver disease.
      (2) after multiple transfusions.
   (g) Cumulative effects (d-tubocurarine, succinyl monocholine).
   (h) Overdosage of antagonists (neostigmine).
   (i) Central depressant action (tubocurarine).
   (j) Combinations of relaxants depolarizing plus non-depolarizing.
   (k) Over-ventilation giving rise to hypocapnia and stimulation of Hering-Breuer reflex.
   (l) Re-distribution of cumulated drug causing re-curarization.
2. Incidental to But Not as Result of Neuroblocking Agent
   ( ) Hypocarbia from over-ventilation.
   (b) Anoxia—cerebral.
   ( ) Hypovolemia with inadequate perfusion of tissues (shock)
   (d) Hypothermia resulting in decreased metabolism or excretion of drug.
   ( ) Depression due to narcotics and other C.N.S. depressants
   (f) Reflex spasm—endotracheal tubes, manipulation of viscera, etc.
3. Bronchospasm
   (a) Histamine release—use antihistamine prior to and epinephrine during.
   (b) Parasympathetic stimulation from antagonists—combine with atropine.
   (c) Instrumentation without obtunding bronchial reflex with topical anesthesia.

C. EXCESSIVE SALIVATION

(a) Parasympathomimetic drugs (neostigmine)
(b) Benzoquinonium.
( ) Inability to swallow due to paresis of muscles (unconscious patients—without atropine).

D SKIN RASHES

(a) Use of salts formed from hydroiodic acid and hydrobromic acid.

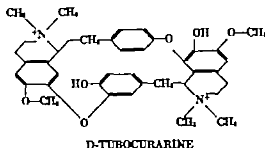
E. INCREASED MUSCLE ACTIVITY

(a) Fasciculations following use of depolarizing drugs.
(b) Increased intra-ocular tension with use of succinyl choline causes tetany of eye muscles.
(c) Muscle pains and aches following depolarizing drugs which cause fasciculations.

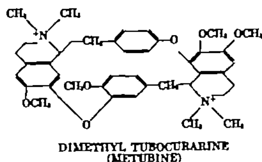
F VISCERAL EFFECTS

(a) Dilated bowel due to ganglionic blockade (d-tubocurarine).

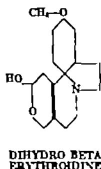
CHEMICAL STRUCTURE OF SKELETAL MUSCLE RELAXANTS



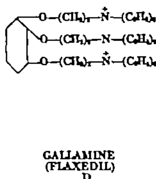
D-TUBOCURARINE



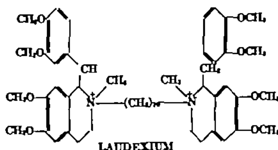
DIMETHYL TUBOCURARINE (METUBINE)



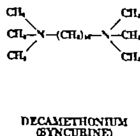
DIHYDRO BETA ERYTHROIDINE



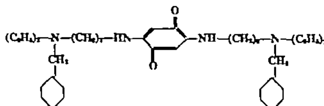
GALLAMINE (FLAXEDIL) D



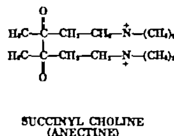
LAUDEXIUM



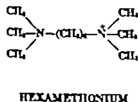
DECAMETHONIUM (SYNCURINE)



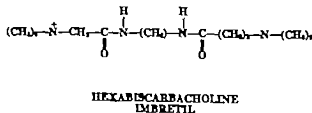
BENZOQUINONIUM (MYTOLON)



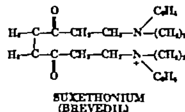
SUCCINYL CHOLINE (ANECTINE)



HEXAMETHONIUM

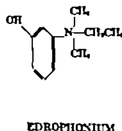


HEXABISCARBACHOLINE IMBRETIL

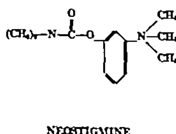


SUXETHONIUM (BREVEDIL)

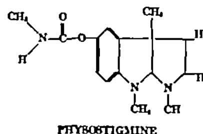
CHEMICAL STRUCTURE OF ANTAGONISTS TO MUSCLE RELAXANTS



EDROPHONIUM



NEOSTIGMINE



PHYSOSTIGMINE

CURARE AND TUBOCURARINE

HISTORY—First report of its use as an arrow poison brought to Europe by Sir Walter Raleigh in 1595. Various preparations derived from miscellaneous plants principally of strychnos family constituted older preparations. Lack of a dependable and identifiable source of drug and absence of standardized specimens interfered with satisfactory clinical use.

SOURCE—Northwest basin of Orinoco Valley. Natives mixed many plants, at least 5 species of strychnos, which were source of earlier specimens. Gill's specimen obtained exclusively from chondrodendron tomentosum a species of menispermaceous plants known to Canelos Indians as "ampi huasca."

APPLICATION OF DRUG—Richard Gill, naturalist and explorer in 1938 brought to United States from South America a curare specimen of identifiable plant origin (chondodendron tomentosum). In 1943 Wintersteiner and Dutcher (Squibb Institute) isolated the active principle, an alkaloid known as d-tubocurarine from the preparation. Authenticated curare was first studied by A. E. Bennett and A. R. McIntyre who introduced its use for shock treatment. First introduced into anesthesiology by H. R. Griffith and G. E. Johnson, Montreal in 1942, subsequently by S. C. Cullen, Iowa, in 1944 at suggestion of Lewis H. Wright, New York. Classical curare effect was first described by Claude Bernard in 1840.

Muscle—Acts by competitive inhibition with acetyl choline. Prevents acetyl choline from acting but has no action of its own. Elevates threshold to acetyl choline at myoneural junction. Injected acetyl choline not effective. Does not inhibit acetyl choline formation at nerve ending. Does not inhibit activity of cholinesterase. Muscle responds to direct electrical stimulation because depression occurs at end plate, but not when nerve is stimulated. Does not change electrical activity of membrane. Does not penetrate into muscle fibre. Exerts no act on smooth muscle.

Somatic Nerve—Conduction not abolished. Acetyl choline liberation not inhibited. Not antagonized by atropine.

Cholinesterase—No effect on ester or enzyme. Physostigmine and neostigmine inhibit cholinesterase, thereby favoring increase of acetyl choline and antagonism of paralytic action. Edrophonium antagonizes blockade by displacing drug from receptor.



Preparation—Barks and stems of plant chondodendron tomentosum extracted with water, then alcohol, evaporated to dryness and made into a sterile solution, having a pH of 4.6 to 4.8. Standardized in rabbits using the "Head Drop Crossover" method. D-tubocurarine chloride pentahydrate is now an accepted standard. One unit of curare equals 0.15 mgm. of alkaloid.

Chemistry—Active principle is the alkaloid d-tubocurarine, quaternary ammonium base which forms a hydrochloride salt. Molecule is broad (pachycurare). Does not enter muscle fibre.

Pharmacology—Acts on receptor substance of striated (voluntary) muscle.

Onset of Action—Intravenously within 2 minutes, intramuscularly 15 minutes, orally no effect unless renal excretion is impaired.

Duration—Varies. In non-narcotized subjects a curarizing dose produces an effect lasting 20 to 30 minutes. With anesthesia action may last 40 to 60 minutes.

Species Variations—Response varies considerably with species. In man produces non-depolarizing block.

USES

1. As an adjuvant to general anesthesia to secure relaxation without causing deep anesthesia.
2. To alleviate muscle spasms in convulsive shock therapy and relief of convulsions caused by excitation of nervous system.
3. As a diagnostic test for myasthenia gravis.
4. To overcome spasm of striated muscle in disease of nervous and muscular origin.
5. To produce respiratory paralysis to induce apnea.
6. To secure relaxation for manipulative procedures, endoscopies of various types and pelvic examinations.
7. To supplement spinal anesthesia when motor effects are passing off.

CONTRAINDICATIONS

1. Myasthenia gravis.
2. Shock from trauma or hemorrhage.
3. Respiratory obstruction, depression or failure.
4. Renal disease.
5. Dehydration accompanied by electrolyte imbalance & deficiency potentiates action.

DISADVANTAGES

1. Paralytic doses cause death by asphyxia.
2. Antidotes not always effective when subject is completely curarized.
3. Action transient.
4. Cumulative effects follow repeated doses.
5. Prolonged use may result in hemoconcentration.
6. Not effective when orally administered.

ADVANTAGES

1. Relaxation obtained at will without deepening anesthesia.
2. Allows lighter plane of anesthesia to be maintained with all agents.
3. Allows mild anesthetics such as N_2O and C_2H_4 to be used for surgery requiring muscular relaxation.
4. Allows use of cyclopropane in upper planes of anesthesia thereby avoiding arrhythmias.
5. Relaxation may be obtained rapidly—within several minutes after administration.
6. No intolerance to repeated uses.

PREPARATION AND DOSES

Chondodendron extract (Intocostrin, curare—20-60 units intravenously in 20 unit fractions of 2 minutes or d-tubocurarine chloride in aqueous solution. Units 20 = 3.0 mgm. = 1 cc

Cerebrum—Subparalytic doses cause no depression. Some depression with paralytic doses. Pain perception, memory and other cerebral reactions remain active. Reaction to pain inhibited due to paralytic action. No change in electro-encephalogram.

Temperature Regulating Center—Not affected.

Vasomotor Center—No significant effect with therapeutic doses.

Vomiting Center—Not depressed. Involuntary muscles involving emesis remain active in unanesthetized subjects.

Respiratory Center—No significant effect with therapeutic doses.

Vagus Nerve—Greater than paralytic doses depress and delay transmission to effector cell.

Cough Center—Not affected. Coughing inhibited due to paresis of thoracic muscles.

Lungs—No effect. No contact of drug with alveoli. Death may result from asphyxia due to paralysis of respiratory muscles without artificial respiration in complete curarization.

Bronchi—No action on bronchi. Bronchoconstrictor action may follow exceptional cases due to histamine-like action of drug.

Metabolism—Reduced due to decreased muscular activity.

Intercostal Muscles—Paralyzed before diaphragm.

Diaphragm—Last voluntary muscle to be paralyzed, first to recover.

Liver—Drug partly detoxified here. Remainder eliminated unchanged by kidney into urine. Effects on hepatic function negligible.

Kidney—Unchanged portion eliminated in the urine. Urinary fraction possesses curare-like action. Cumulative action follows use in renal damage. Same is true of tubocurarine. Second dose more effective than first dose even when effects of first dose are gone.

Body Temperature—Reduced due to decreased muscular activity.

Blood—No significant effects. After prolonged administration hemoconcentration followed by circulatory collapse occurs.

Skin—Perception of pain and other sensation not abolished. No sweating. May produce typical histamine wheals.

Tissues—No tissue changes ascribable to drug.

Eyes—No effect on pupils. Muscles of lids and eyeballs first to be involved. Heaviness of lids, ptosis, diplopia, nystagmus follow in order in conscious subjects. Relaxation and cessation of eyeball movements in anesthetized subjects.

Facial Nerve—Next to the eye in involvement. Causes mask-like expression on face.

Trigeminal Nerve—Not affected—purely sensory.

Salivary Glands—Secretions continue to form in unanesthetized patient.

Neck Muscles—Depressed after cranial nerves.

Pharynx—"Gag" reflex abolished due to loss of motor control of pharyngeal muscles.

Muscles of Swallowing—Affected early. Saliva and other secretions accumulate in pharynx due to absence of power of deglutition.

Larynx—Coughing abolished due to loss of expulsive power from paresis of thoracic muscles. Vocal cords relaxed. Sensory effects of larynx not affected.

Heart—No significant effects. No effects on electrocardiogram. Does not prevent arrhythmias.

Blood Pressure—Therapeutic doses cause no significant effects.

Stomach—Decreased tone. Decrease in peristalsis. Drug probably destroyed in gastrointestinal tract. Ineffective orally.

Intestines—Paralytic doses decrease muscle tone and peristalsis.

Uterus—Not relaxed by therapeutic doses. Believed to pass into placental circulation.

Muscles of Extremities—Affected after the abdominal and thoracic muscles.

Muscle Fibres—React to electrical stimulation. No direct effect on muscle.

Nerve Ending—No effect. No inhibition of acetyl choline production.

Autonomic Nervous System—Causes a depression of (from pre- to post ganglionic fibres) conduction through autonomic ganglia both sympathetic and parasympathetic. Does not prevent liberation of acetyl choline when preganglionic fibre is stimulated. Large dose may also prevent transmission from postganglionic fibres to effector cell.

THE ACTIONS OF CURARE ARE ESSENTIALLY THOSE OF TUBOCURARINE

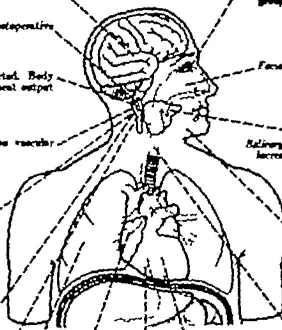
SUCCINYL CHOLINE

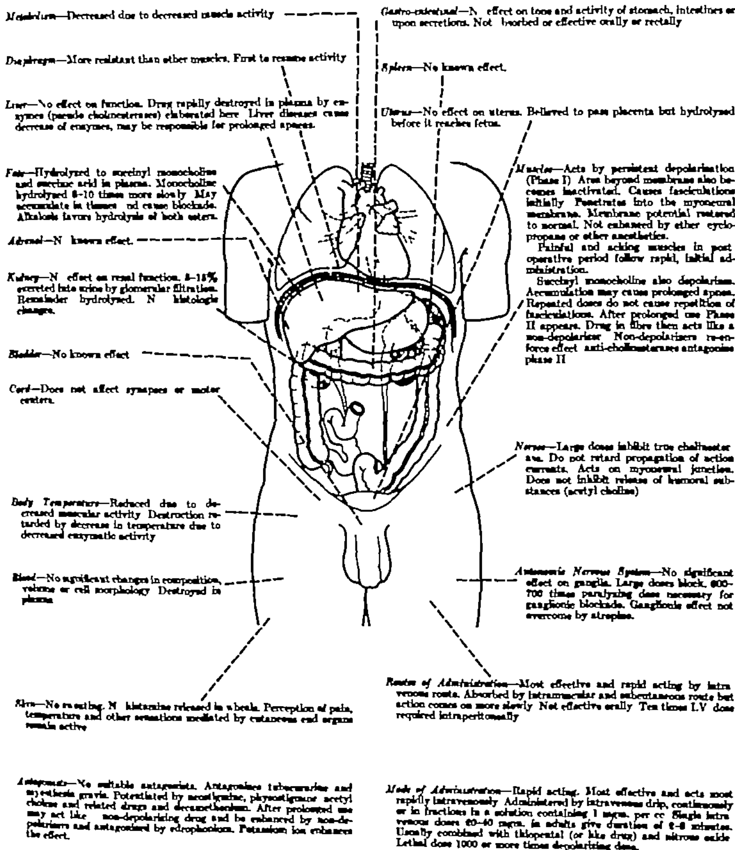
SYNONYMS—Anectine (Wellcome) suxamethonium, Quelicin, Sucostrin (Squibb)

HISTORY—First studied in curarised animals by Hunt and Taveau in 1911 and thereby muscle relaxant effects were overlooked. Relaxant effects discovered by Bovet and co-workers in 1951. Numerous investigators have studied action since then. (Foldes et al.)

CHEMISTRY—A di-quaternary base consisting of two acetyl choline molecules fused together. Addition of carboxyl groups to a quaternary base shortens duration of action. Nitrogen atoms 14Å apart.

PROPERTIES—White odorless, slightly bitter powder. Forms a hydrate which melts at 156°-160°. Very soluble in water, slightly soluble in benzene and chloroform, insoluble in ether. Prepared as the di-hydrochloride and di-iodide. pH of 2% solution varies between 2-3. Incompatible with alkalis, thiopental and other sodium barbiturate solutions. Chloride preferred—does not cause iodism. Iodide ⅔ as potent (1 mg. = 1 mg.) as hydrochloride. Stable sterilized by autoclaving. Solutions lose potency unless refrigerated.




Metabolism—Decreased due to decreased muscle activity
Diaphragm—More resistant than other muscles. First to resume activity
Liver—No effect on function. Drug rapidly destroyed in plasma by enzymes (pseudo cholinesterases) elaborated here. Liver diseases cause decrease of enzymes, may be responsible for prolonged apnea.
Fate—Hydrolyzed to succinyl monocholine and succinic acid in plasma. Monocholine hydrolyzed 6-10 times more slowly. May accumulate in tissues and cause blockade. Alkalosis favors hydrolysis of both esters.
Adrenal—No known effect.
Kidney—No effect on renal function. 8-15% excreted into urine by glomerular filtration. Remainder hydrolyzed. No histologic changes.
Bladder—No known effect
Cord—Does not affect synapses or motor centers.
Body Temperature—Reduced due to decreased muscular activity. Destruction retarded by decrease in temperature due to decreased enzymatic activity
Blood—No significant changes in composition, volume or cell morphology. Destroyed in plasma
Gastro-intestinal—No effect on tone and activity of stomach, intestines or upon secretions. Not absorbed or effective orally or rectally
Spleen—No known effect.
Uterus—No effect on uterus. Believed to pass placenta but hydrolyzed before it reaches fetus.
Muscles—Acts by persistent depolarization (Phase I). Area beyond membrane also becomes inactivated. Causes fasciculations initially. Penetrates into the myoneural membrane. Membrane potential restored to normal. Not enhanced by ether cyclopropane or other anesthetics.
Painful and aching muscles in post operative period follow rapid, initial administration.
Succinyl monocholine also depolarizes. Accumulation may cause prolonged apnea. Repeated doses do not cause repetition of fasciculations. After prolonged use Phase II appears. Drug in fibre then acts like a non-depolarizer. Non-depolarizers re-enforce effect. anti-cholinesterases antagonize phase II
Nerves—Large doses inhibit true cholinesterase. Do not retard propagation of action currents. Acts on myoneural junction. Does not inhibit release of humoral substances (acetyl choline)
Autonomic Nervous System—No significant effect on ganglia. Large doses block. 600-700 times paralyzing dose necessary for ganglionic blockade. Ganglionic effect not overcome by atropine.
Skin—No reaction. No histamine released in wheals. Perception of pain, temperature and other sensations mediated by cutaneous end organs remain active
Routes of Administration—Most effective and rapid acting by intravenous route. Absorbed by intramuscular and subcutaneous route but action comes on more slowly. Not effective orally. Ten times I.V. dose required intraperitoneally
Antagonists—No suitable antagonists. Antagonizes tubocurarine and myasthenia gravis. Potentiated by neostigmine, physostigmine, acetyl choline and related drugs and decamethonium. After prolonged use may act like non-depolarizing drug and be enhanced by non-depolarizers and antagonized by edrophonium. Potassium ion enhances the effect.
Mode of Administration—Rapid acting. Most effective and acts most rapidly intravenously. Administered by intravenous drip, continuously or in fractions in a solution containing 1 mgm. per cc. Single intravenous doses 20-40 mgm. in adults give duration of 2-6 minutes. Usually combined with thiopental (or like drug) and nitrous oxide. Lethal dose 1000 or more times depolarizing dose.

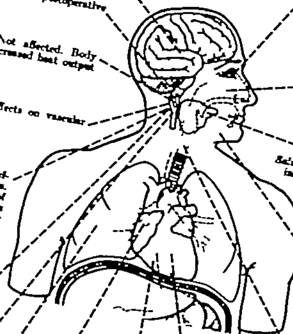
SUCCINYL CHOLINE

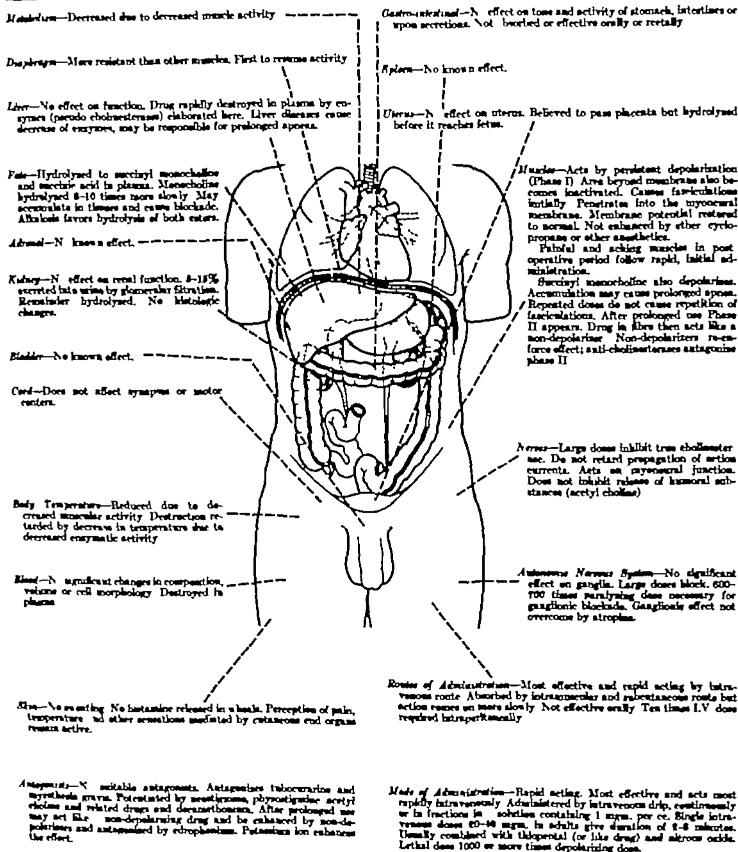
SYNONYMS—Anectine (Wellcome) suxemethonium, Quelicin, Sucostrin (Squibb)

HISTORY—First studied in curarized animals by Hunt and Taveau in 1911 and thereby muscle relaxant effects were overlooked. Relaxant effects discovered by Bovet and co-workers in 1951 Numerous investigators have studied action since then. (Foldes et al.)

CHEMISTRY—A di-quaternary base consisting of two acetyl choline molecules fused together Addition of carboxyl groups to a quaternary base shortens duration of action. Nitrogen atoms 14Å apart.

PROPERTIES—White, odorless, slightly bitter powder Forms a hydrate which melts at 156°–160° Very soluble in water slightly soluble in benzene, and chloroform, insoluble in ether Prepared as the di-hydrochloride and di-iodide. pH of 2% solution varies between 2–3 Incompatible with alkalis, thiopental and other sodium barbiturate solutions. Chloride preferred—does not cause iodism. Iodide ⅞ as potent (1 mg. = 1 mg.) as hydrochloride Stable, sterilized by autoclaving. Solutions lose potency unless refrigerated.

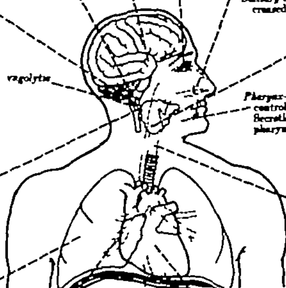


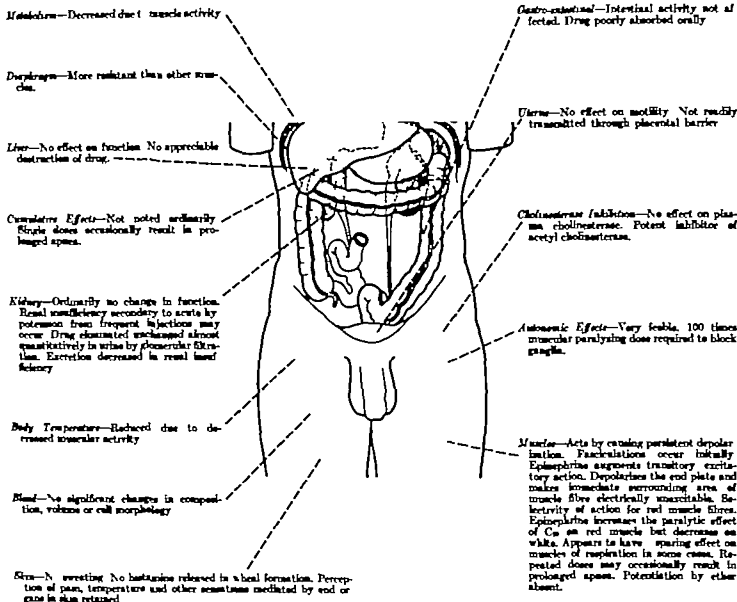

Metabolism—Decreased due to decreased muscle activity
Diaphragm—More resistant than other muscles. First to resume activity
Liver—No effect on function. Drug rapidly destroyed in plasma by enzymes (pseudo cholinesterases) elaborated here. Liver diseases cause decrease of enzymes, may be responsible for prolonged apnea.
Fate—Hydrolysed to succinyl monocholine and succinic acid in plasma. Monocholine hydrolysed 6–10 times more slowly. May accumulate in tissues and cause blockade. Alkalosis favors hydrolysis of both esters.
Adrenal—No known effect.
Kidney—No effect on renal function. 8–15% excreted into urine by glomerular filtration. Remainder hydrolysed. No histologic changes.
Bladder—No known effect.
Cord—Does not affect synapses or motor centers.
Body Temperature—Reduced due to decreased muscular activity. Destruction retarded by decrease in temperature due to decreased enzymatic activity
Blood—No significant changes in composition, volume or cell morphology. Destroyed in plasma
Skin—No sweating. No histamine released in wheals. Perception of pain, temperature and other sensations mediated by cutaneous end organs remain active.
Antagonists—No suitable antagonists. Antagonizes tubocurarine and myasthenia gravis. Potentiated by neostigmine, physostigmine, acetyl choline and related drugs and decamethonium. After prolonged use may act like non-depolarizing drug and be enhanced by non-depolarizers and antagonized by edrophonium. Potassium ion enhances the effect.
Gastro-intestinal—No effect on tone and activity of stomach, intestines or upon secretions. Not absorbed or effective orally or rectally
Spleen—No known effect.
Uterus—No effect on uterus. Believed to pass placenta but hydrolysed before it reaches fetus.
Muscles—Acts by persistent depolarization (Phase I). Area beyond membrane also becomes inactivated. Causes fasciculations initially. Penetrates into the myoneural membrane. Membrane potential restored to normal. Not enhanced by ether cyclopropane or other anesthetics.
Painful and aching muscles in post operative period follow rapid, initial administration.
Succinyl monocholine also depolarizes. Accumulation may cause prolonged apnea. Repeated doses do not cause repetition of fasciculations. After prolonged use Phase II appears. Drug in fibre then acts like a non-depolarizer. Non-depolarizers re-enforce effect; anti-cholinesterases antagonize phase II
Nerves—Large doses inhibit true cholinesterase. Do not retard propagation of action currents. Acts on myoneural junction. Does not inhibit release of humoral substances (acetyl choline)
Autonomic Nervous System—No significant effect on ganglia. Large doses block. 600–700 times paralyzing dose necessary for ganglionic blockade. Ganglionic effect not overcome by atropine.
Routes of Administration—Most effective and rapid acting by intravenous route. Absorbed by intramuscular and subcutaneous route but action comes on more slowly. Not effective orally. Ten times I.V. dose required intraperitoneally
Mode of Administration—Rapid acting. Most effective and acts most rapidly intravenously. Administered by intravenous drip, continuously or in fractions in solution containing 1 mgm. per cc. Single intravenous doses 20–40 mgm. in adults give duration of 2–8 minutes. Usually combined with thiopental (or like drug) and nitrous oxide. Lethal dose 1000 or more times depolarizing dose.

DECAMETHONIUM (SYNCURINE)

SYNONYMS—Syncurine C_{10}

CHEMISTRY AND PROPERTIES—A bi-quaternary base composed of 10 carbon atoms in a straight chain with a quaternary nitrogen atom on each terminal carbon Three methyl groups on nitrogen atom. Forms halides with hydrobromic hydrochloric and hydroiodic acid Water soluble Preparation contains 1 mgm. per cc. Solution is stable Non-irritating to the tissues. Compatible with barbiturates (thiopental) in the same solution.





ANTAGONISM—Neostigmine and edrophonium of no value as antagonists. May enhance effect. Antagonizes depolarizing action. Small doses stimulate end plate of myasthenics.

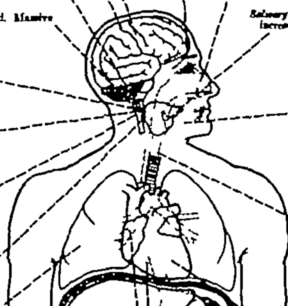
DOSE—Initial dose of 2 to 3 mgm. at 1 mgm. per minute intravenously. On a weight basis four times more potent than d-tubocurarine. Onset of action same as d tubocurarine. Duration of action is shorter. May cause tachyphylaxis.

GALLAMINE (FLAXEDIL)

SYNONYMS—Flaxedil, TRIEG

HISTORY—Synthesized and studied pharmacologically by Bovet and his associates in 1946 (Italy) Introduced into therapy by Huguenard (1948) First synthetic substitute for curare.

CHEMISTRY—A tri-quaternary base Chemical name 1 2-3 tridiethyl amino ethoxy benzine Available as a tri-iodide or tri-chloride salt. White colorless, water-soluble stable powder Acid in reaction. Each cc. contains 20 mgm.



Metabolism—Decreased due to decreased muscle activity

Autonomic Nervous System—No significant effect on ganglia. Autonomic ganglia blocking activity negligible. Visceral structures innervated by autonomic nerves not significantly affected.

Diaphragm—More resistant than other muscle groups. Last to lose its activity and first to regain it.

Gastro-intestinal—No appreciable effect on tone or motility. Not absorbed from gastro-intestinal tract.

Liver—No effect on function. Some destruction by the liver (less than 30%).

Adrenal—No known effect.

Uterus—Motility not affected. Passes placental barrier to fetus.

Kidney—No effect on renal function. Greater portion (70-100%) of an intravenous dose excreted into the urine within two hours. No histopathologic changes on renal parenchyma.

Muscles—Acts competitively with acetylcholine at myoneural receptors. No fasciculation initially. Potentiated by ether. Order of paralytic involvement of different muscle groups similar to tubocurarine.

Spinal Cord—Synaptic transmission in the cerebrospinal axis unaffected.

Bladder—No known effect.

Blood—No significant changes in composition, volume or cellular morphology.

Body Temperature—Reduced due to decreased muscular activity. Elimination retarded by decrease in temperature due to decreased peripheral circulation.

Skin—No sweating. No histamine release (wheals). Perception of pain, temperature and other sensations mediated by end organs in skin remain active.

ADMINISTRATION—Onset immediate and maximal within four minutes given intravenously. The usual dose 1 mgm. per kilogram of body weight. Inactive orally. Absorbed subcutaneously in the muscles but slower. Cumulative *effects* result from repeated administration.

POTENCY—On a weight basis ⅕ as potent as d-tubocurarine. Duration of action is slightly shorter.

ANTAGONISM—Prior dose prevents paralytic effect of decamethonium. Antagonized by anticholinesterases (neostigmine and edrophonium).

MARGIN OF SAFETY—Comparable to d-tubocurarine.

CURARE 1

Name	Tubocurarine	Di methyl ether of tubocurarine (methyl tubocurarine)	Gallamine triethiodide	Decamethonium	Benzoquinonium	Succinyl choline
Synonym	—	Mecostrin Metubine	Flaxedil	Syncurine, C10	Mytolon—Win 2747	Anectine
History	Isolated by Wintersteiner and Dutcher in 1943 and King in 1935	Studied by K. K. Chen et al, 1949	Studied by Bovet et al in 1947	Studied by Paton and Zaimis, and Organe	Studied in 1951 by Hoppe et al	Prepared by Hunt & Taveau in 1911, by Bovet 1951
Source	Alkaloid of Curare	Synthetic from tubocurarine	Synthetic	Straight chain of ten carbon atoms with nitrogen at each end	2,5 bis (3 diethyl amino propylamino) benzoquinone bis (benzyl chloride)	Synthetic
Chemistry	Quarternary ammonium base	Quarternary ammonium base	Tri (diethyl amino ethoxy) benzene triethyl iodide	Quarternary base	Quaternary base	Ester of [illegible] choline
Number of Nitrogen atoms	8–14Å units apart	8–14Å units apart	8–14Å units apart	8–14Å units apart	8–14Å units apart	8–14Å units apart
Stability	Stable	Stable	Stable	Stable, [illegible]	Stable and solid, soluble in H_2O. Inactivated by copper or brass	Stable, [illegible]
Onset of action I.V.	1½ min.	1–2 min.	About 2 min	About 4 min.	About 2 min.	1–2 min.
Onset of action I.M.	5–10 min.	5–10 min.	5–10 min.	5–10 min.	Effective in 10–15 min.	2–4 min.
Oral	No effect	No effect	—	—	Effective	—
Peak effect	3–7 min. I.V.	3–7 min. I.V.	3 min. I.V.	10–15 min.	6–10 min.	2–4 I.V.
Duration	20–25 min.	25–90 min.	20–40 min.	8–15 min.	10–15 min.	2–8 min.
Mode of action	Prevents depolarizing action of acetyl choline at skeletal muscle nerve endings	Same as tubocurarine	Prevents depolarization action of acetyl choline at nerve endings	Causes persistent depolarization at nerve endings of skeletal muscle	Not known exactly	Causes persistent [illegible]
Central effect	None ordinarily	None ordinarily	None	None	None	None
Analgesic effects	None	None ordinarily	None	None	None	None
Mucous secretions	Continues to form without atropine	Continues to form without atropine	Continues to form without atropine	Not increased	Quite pronounced	Not increased
Cardiovascular effect	Blood pressure may fall	Same as tubocurarine	No effect on B.P. Increases heart rate	Blood pressure may fall	Bradycardia and fall in B.P. [illegible] may occur	—
Blood volume	Hemo-concentration over prolonged use	—	—	—	—	—
Blood chemistry	No change	No change	No change	No change	No change	No change
Effects on respiration	Apnea 1 [illegible] Paralysis of muscles 1 [illegible]	Apnea [illegible] Paralysis of muscles [illegible]	Apnea 1.5 Paralysis 1 [illegible]	Apnea 1.5 Resp. muscle paralysis 1 [illegible]	Minimal respiratory depression	Apnea [illegible] Resp. paralysis 1 [illegible]
Histamine like action	Present	Present	Not present	Not present	Not present	None
Effects on kidney	No known effect	No known effect	No known effect	No known effect	No known effect	No known effect
Effects on liver	No known effect	No known effect	No known effect	No known effect	No known effect	No known effect
Effects on smooth muscle	No known direct effect	No known direct effect	No known direct effect	No direct effect	No direct effect Vagal effect	Not significant
Fasciculations	None	None	None	Occurs	None	Occurs
Placental transmission	Passes to fetus	Transmitted	Transmitted	—	—	—
Effects of edrophonium (tensilon) and neostigmine	Antagonized by these. Also by K	Antagonized by these. Also by K	Antagonized by these	Effects enhanced. Not [illegible]. Not antagonized by K	Not suitable. Neostigmine enhances vagal effects	Effects enhanced [illegible]. Do not antagonize
Potentiation by ether	Potentiated 2 to 3X	Potentiated 2 to 3X	Not potentiated	Not potentiated	Potentiated	Not potentiated
Effect of repeated dose	Cumulative action	Present	No tachyphylaxis	Cumulative action Tachyphylaxis present	Effective	Active. No cumulative effect
Use with anesthesia	Very useful	Very useful	Useful	Useful	Useful	Very useful
Use with atropine	Compatible	Compatible	Has vagolytic effect	May be used	Antagonizes	May be used
Ganglionic effects	Causes block in large doses	Present	None or slight	None or slight	Vagal depressor None	Not significant
Postganglionic effects	Large doses depress vagus	Same as tubocurarine	Vagolytic action	None	Vagal depressor	Not significant
Elimination	Almost all unchanged in the urine	Into urine	Usual dose eliminated in 2 hrs	—	Into urine [illegible] urine and	Rapidly hydrolyzed ([illegible]) by
Dose	6–15 mgm. I.V.	2–4 mgm. I.V.	40–60 mgm. I.V.	4.0 mgm. I.V.	6–15 mgm.	20 mgm. single or [illegible] drip continuous
Toxicity	Larger than curarizing doses toxic	Larger than curarizing doses toxic	Larger than curarizing doses toxic 2 hrs	—	Large doses cause severe vagal effects	Larger than usual doses not harm vascular system
Effect on tumors	None	None	—	None	None	None
Compatibility with other drugs	Precipitated by alkaline solutions	Precipitated by alkaline solutions	Precipitated by alkaline solutions	May be mixed with thiopental	Precipitated by alkaline solutions	Inactivated. Precip. by alkaline solutions

41 MUSCLE RELAXANTS

Erythroidine	Mephenesin	Quinine derivatives	Laudexium	Hexacarbacholine	Suxethonium	Hexafluoreni[...]
Erythroidine	Tolserol, myanesin	—	Laudolissin	Imbretil	Brevedil "E"	Mylaxen
Studied by Unna in 1944	Studied by Berger and Bradley 1946	Quinine and derivatives made by substituting alkyl radicals to nitrogen atoms of quinine have been studied.	Prepared by Taylor and Collier 1951. Used by Bodman 195[illegible]	Prepared by Cheymol 19[illegible]	Synthesized by Bovet and associates. Used by Valdoni 1949	Studied by [...] [illegible] and Ar[...]
Synthetic. Made from beta erythroidine found in erythrina plants	Synthetic	Made synthetically from quinine	Synthetic	Synthetic	Synthetic	Synthetic
Dihydro beta erythroidine	3 ortho toloxy-1,2 propanediol	—	Resembling tubocurarine. Has [illegible] molecule.	6 carbon chain with two carbamoyl-choline groups at each end.	Same as succinyl choline except one ethyl group replaces methyl on each nitrogen atom.	Hexamethyl[...] (9 fluorenyld[...] [illegible]) di[...]
Contains one tertiary nitrogen atom	Contains no nitrogen atom	Quaternary bases	Two quaternary nitrogen atoms separated by ten carbons in chain.	Two quaternary separated by ten atoms.	Two quaternary	Two quat[...] rated by 6 c[...]
Stable, boilable	Stable, boilable, but poorly soluble in H_2O	Stable	Stable substance forms methyl sulphate. pH 4.5	Very stable. Hydrolyzed slowly	Forms di-iodide salt. Melts at 185°C.	Forms stab[...] salts.
1-3 min.	3-5 min.	Slow onset. Not used	Slower than tubocurarine	Slightly longer than succinyl choline. 1½-2 minutes	Similar to succinyl choline	2-3 minutes.
[illegible]	Not used	Quinine usually given orally	Slower than tubocurarine	Slower	30-40 seconds	2-3 minutes.
Effective 5-10 min. I.V.	30 min. 5 min. I.V.	Several hours —	Not absorbed. Requires longer time to reach it than tubocurarine	Not used Lasts 1-3 hrs.	Not used. 1 1½ minutes	Not effective Relaxant [...] only during [...]
30-60 min. Same as tubocurarine	3-7 min. I.V. Blocks at internuncial neurons in spinal cord	— Blocks at nerve ending. Prolongs refractory period of striated muscle	— Non-depolarizing, like tubocurarine.	— Non-depolarizing action	— Depolarizing	Not known Lipophilic [...] trates with [...]
Central depression with greater than curarizing doses	Depresses thalamus and cortex	None	None	None	None	None
None	Produces local anesthetic action	None	None	None	None	None
Continues to form	Does not enhance	None	No increase. Continues to form	No increase. Continues to form	No increase. Continues to form	No increase. to form
Causes hypotension	Large doses depress S.A. Node	None	None	None	None	None
—	—	—	None	None	No change	—
— Same as curare	No known change Not ordinarily. Massive doses paralyze	No change Do not paralyze ordinarily	No changes Does not completely relax cords	No changes Apnea	No changes Like succinyl choline	— Acts with [...] bone or other
Does not occur No known effect No known effect No significant effect	None No known effect No known effect May relax intestine	None None None Slight	Less than tubocurarine Flattened slowly None None	None None None	None None None None	None None None None
None —	None —	None Not studied	Not present —	None —	Less than succinyl choline	None Has poor power
Antagonizes	No effect	—	Antagonized by it	Antagonized by it	Not antagonized by	Acts as anti[...] ase. Not anta[...]
Potentiated	None	—	Marked effect	—	None	Only acts d[...] throm
No cumulative effect or tachyphylaxis	No cumulative effect	Some cumulative action	Cumulative effects	Cumulative	Not cumulative	Potentiated [...] choline
Useful	Very transient Not suitable	Not useful. Quinine used for myotonia	Long lasting 1-3 hrs.	Long lasting. 1-3 hrs.	Shorter acting than succinyl choline.	Effective onl[...] oral anesthe[...]
Antagonizes bradycardia May be used	May be used	May be used	May be used	May be used	May be used	May be used
Not known Not known Into urine	No significant effect No significant effect Detoxified by conjugation by liver. Part eliminated unchanged	— — Not studied	Less than d-tubocurarine No significant effects —	Less than tubocurarine None —	Insignificant Insignificant Hydrolyzed by plasma cholinesterase	None None —
30-75 mgm. Initial—100 average 10X more toxic and 6X more potent than erythroidine	0.25-1 gm. of q 4h orally Wide margin of safety	Methochloride—8-10 mgm. per kgm. Wide margin of safety	75% potency of d-tubocurarine Long lasting	.05 mgm. Kgm. Potent and long lasting	60-80 mgm. Like succinyl choline	10 mgm. frac[...] I.V. .20% sol[...] Low toxicity
No known effect Precipitated by alkaline solutions	No known effect Miscible with alkaline substances	Locally irritating Precipitated by alkaline solutions	None Precipitated by alkaline solutions	None —	None Not miscible with thiopental	None Precipitated solutions

ANTICURARE DRUGS (ANTICHOLINESTERASES)

Non-depolarizing relaxants antagonized by compounds which have (1) anticholinesterase effect or (2) have direct depolarizing action at myoneural junction. Anticholinesterases inhibit hydrolysis of acetyl choline and overcome curare effect by mass action. Anticholinesterases enhance effects of depolarizers (decamethonium) May reverse depolarizing effect of mixed block (phase II of block) by depolarizing agents. Anticholinesterases produce concomitant cholinergic effects in autonomic nervous system. Prevented by concomitant or prior administration of atropine

Anticholinesterases may fail to re-establish block if (1) end plate receptors have lost affinity for acetyl choline, (2) pathological fixation of blocking agent at receptor (3) if an excess of acetyl choline forms which produces a depolarizing block of its own, (4) if prolonged depolarization of end plate by depolarizing drug is present.

Cholinesterase is an enzyme protein with 2 active sites—an anionic and an esteractic. Acetyl choline is bound at anionic site electrostatically The carbonyl group binds at esteractic site to form an intermediate ester complex This reacts with water and breaks up the ester linkage Compounds like acetyl choline capable of producing quaternary ammonium ions, combine at the anionic site They inhibit the enzyme competitively Compounds with a carbonyl group (neostigmine a carbamate) combine at esteractic site to form ester type groupings. Acetyl choline joins at esteractic site to form readily hydrolyzable compound. Ester group formation with anticholinesterases, therefore compete with acetyl choline for place at esteractic site

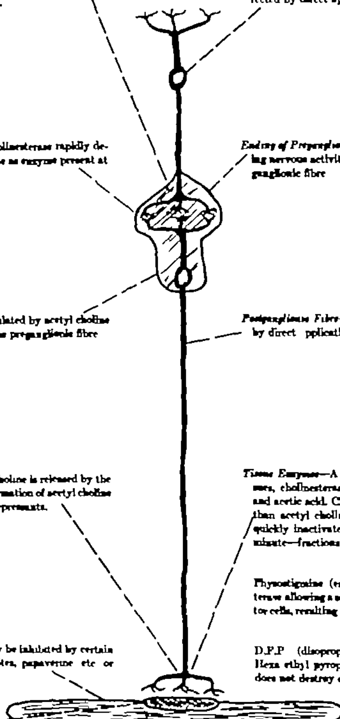
Chemically three principal types compounds exhibit anticholinesterases activity (1) alkyl and aryl carbamates (Neostigmine Pyridostigmine (Mestinon)) (2) quaternary ammonium ions (Edrophonium) (3) alkyl or aryl phosphates or fluorophosphates. These phosphates cause irreversible unions. Not suitable as anticurare agents.

Name	Edrophonium	Physostigmine	Neostigmine
Synonym	Tensilon	Eserine	Prostigmine
Source	Synthetic	Alkaloid from Calabar bean.	Synthetic
Chemical	A quaternary base 3, hydroxy phenyl, dimethyl ammonium bromide. Has no carbamic acid grouping to attach to esteractic portion of cholinesterase.	Tertiary amine containing methyl carbamic group attached to aromatic ring.	A trimethylated quaternary ammonium ion as well as a substituted carbamic acid ester, attached to both ionic and esteractic grouping of cholinesterase.
Mechanism of Action	Feeble anticholinesterase action. Is quaternary ammonium base which excites neuromuscular apparatus. Reestablishes transmission at neuromuscular junction by acting competitively with curare and displacing it from end plate. Enhances any existing depolarization.	Combines reversibly with cholinesterase. Onset of action gradual. Due to acetyl choline build-up	Inhibits cholinesterase competitively Reversible. Lasts 2–4 hours. Also has excitatory action on the neuromuscular apparatus. Massive doses cause some ganglionic blockade.
Distribution in Body	Does not penetrate epithelial or lipoid barriers. Quaternary base—does not penetrate.	Penetrates lipoid structures. Passes through epithelium.	Poorly absorbed—a quaternary base. Does not penetrate epithelial or lipoid barriers.
Action on Skeletal Muscle	Competitive displacement of curare at end-plate. Reverses the action of curare. Fasciculations in large doses. Anticholinesterase activity of minor consequence.	Causes fasciculations in large doses.	Reverses the action of curare and similar drugs. Fasciculations in large doses if used alone.
Central Effects	None Does not penetrate into nervous tissues.	Intense increase in brain activity E.E.G pattern shows increased activity	None. Does not penetrate into nervous tissues.
Autonomic Effects	Action similar t parasympathetic stimulation. Antagonized by atropine.	Manifests effects of parasympathetic stimulation by permitting accumulation of acetyl choline. Antagonized by atropine.	Manifests effects of parasympathetic stimulation. Antagonized by atropine.
Dose	5–10 mgm. I.V Action transient. Recurarization of displaced curare t end plate may occur Requires repeated doses. Action not cumulative.	Physostigmine Salicylate. Dose 0.5–1.0 mgm. Generally not suitable for severe over curarization.	Neostigmine Bromide tablets 15–30 mgm Neostigmine methyl sulphate for I.V use. Dose 0.5–1.0 mgm.

THE PHARMACOLOGIC BEHAVIOR OF CHOLINERGIC (PARASYMPATHETIC) POSTGANGLIONIC AUTONOMIC FIBRES

Ganglion—Stimulated by nicotine at first, then depressed. Depressed by ganglionic blocking agents such as etamon and other alkyl substituted ammonium halides, banthine and by direct application of local anesthetics.

Preganglionic Fibres—Arise in cord and pass to autonomic ganglia. Nervous impulses arising in cord are transmitted to the ganglion which synapses with postganglionic fibre Affected by direct application of local anesthetics.



Tissue Enzymes—A specific enzyme cholinesterase rapidly destroys the acetyl choline formed. Same as enzyme present at postganglionic nerve endings.

Ending of Preganglionic Axone—Acetyl choline is released during nervous activity at this site Stimulates dendrite of post ganglionic fibre

Dendrite of Postganglionic Fibre—Stimulated by acetyl choline thereby relaying the impulse from the preganglionic fibre

Postganglionic Fibre—Transmits impulses t organs. Blocked by direct pplication of local anesthetic drugs.

Postganglionic Nerve End ng—Acetyl choline is released by the impulse traveling down the fibre. Formation of acetyl choline not inhibited by parasympathetic depressants.

Tissue Enzymes—A specific enzyme present in serum or tissues, cholinesterase, hydrolyses acetyl choline into choline and acetic acid. Choline is approximately 1/1000 less active than acetyl choline Hydrolysis is rapid and substance is quickly inactivated. Amount of acetyl choline liberated is minute—fractions of a milligram.

Physostigmine (eserine) and prostigmine inhibit cholinesterase allowing a sustained action by acetyl choline on effector cells, resulting in prolonged parasympathetic stimulation

Glandular or Muscular Structure—May be inhibited by certain drugs—syntropan, trasentine altrites, papaverine etc or stimulated by barium, pituitrin, et

D.F.P (diisopropyl fluorophosphat) destroys enzyme Hexa ethyl pyrophosphat yields prolonged inhibition but does not destroy enzyme

Receptor Substance—Acetyl choline passes t junctional tissue and stimulates glandular or muscular structure Threshold to acetyl choline elevated by banthine atropine scopolamine hyoscyamine homatropine novatropine and other tropeines. Parasympathetic depression results. Choline derivatives, methyl acetyl choline carbamino acetyl choline etc stimulate also Parasympathetic stimulation results.

ANTICURARE DRUGS (ANTICHOLINESTERASES)

Non-depolarizing relaxants antagonized by compounds which have (1) anticholinesterase effect or (2) have direct depolarizing action at myoneural junction. Anticholinesterases inhibit hydrolysis of acetyl choline and overcome curare effect by mass action. Anticholinesterases enhance effects of depolarizers (decamethonium). May reverse depolarizing effect of mixed block (phase II of block) by depolarizing agents. Anticholinesterases produce concomitant cholinergic effects in autonomic nervous system. Prevented by concomitant or prior administration of atropine.

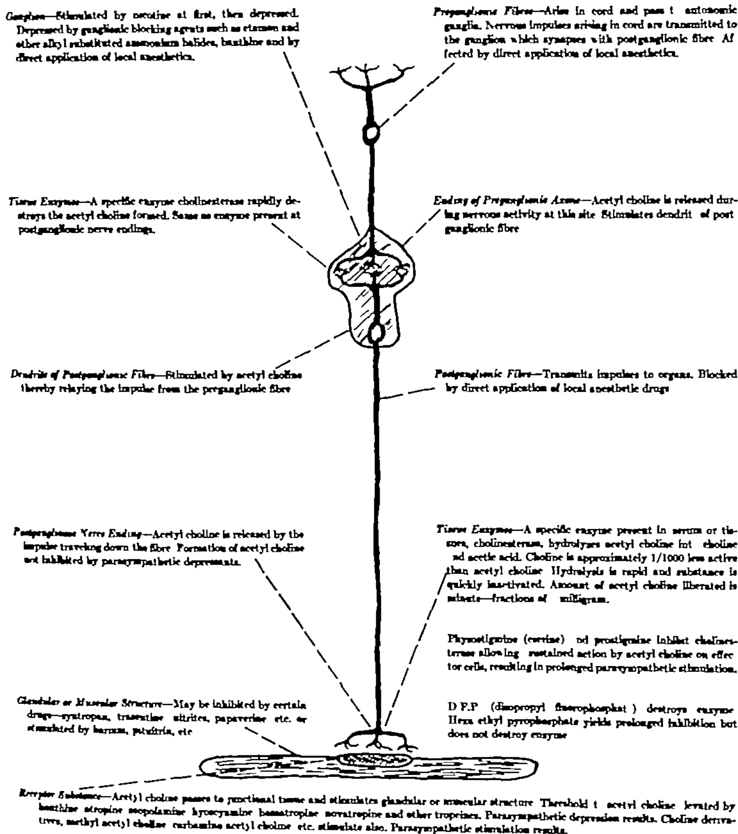
Anticholinesterases may fail to re-establish block if (1) end plate receptors have lost affinity for acetyl choline (2) pathological fixation of blocking agent at receptor (3) if an excess of acetyl choline forms which produces a depolarizing block of its own, (4) if prolonged depolarization of end plate by depolarizing drug is present.

Cholinesterase is an enzyme protein with 2 active sites—an anionic and an esteractic. Acetyl choline is bound at anionic site electrostatically. The carbonyl group binds at esteractic site to form an intermediate ester complex. This reacts with water and breaks up the ester linkage. Compounds like acetyl choline, capable of producing quaternary ammonium ions, combine at the anionic site. They inhibit the enzyme competitively. Compounds with a carbonyl group (neostigmine a carbamate) combine at esteractic site to form ester type groupings. Acetyl choline joins at esteractic site to form readily hydrolyzable compound. Ester group formation with anticholinesterases, therefore, compete with acetyl choline for place at esteractic site.

Chemically three principal types compounds exhibit anticholinesterases activity (1) alkyl and aryl carbamates (Neostigmine, Pyridostigmine (Mestinon)) (2) quaternary ammonium ions (Edrophonium) (3) alkyl or aryl phosphates or fluorophosphates. These phosphates cause irreversible unions. Not suitable as anticurare agents.

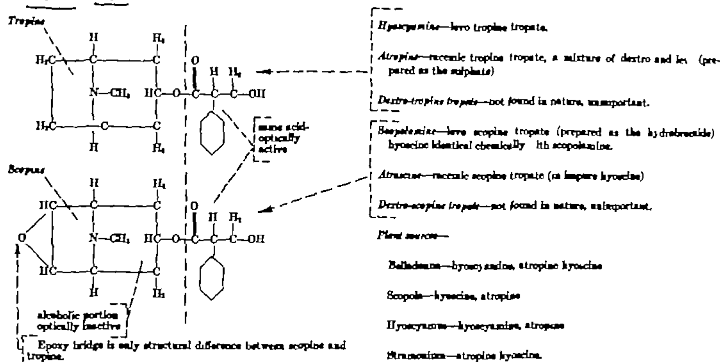
Name	Edrophonium	Physostigmine	Neostigmine
Synonym	Tensilon	Eserine	Prostigmine
Source	Synthetic	Alkaloid from Calabar bean.	Synthetic
Chemical	A quaternary base. 3, hydroxy phenyl, dimethyl ammonium bromide. Has no carbamic acid grouping to attach to esteractic portion of cholinesterase.	Tertiary amine containing a methyl carbamic group attached to aromatic ring.	A trimethylated quaternary ammonium ion as well as a substituted carbamic acid ester attached t both ionic and esteractic grouping of cholinesterase.
Mechanism of Action	Feeble anticholinesterase action. Is quaternary ammonium base which excites neuromuscular apparatus. Reestablishes transmission at neuromuscular junction by acting competitively with curare and displacing it from end plate. Enhances any existing depolarization.	Combines reversibly with cholinesterase. Onset of action gradual. Due to acetyl choline build-up.	Inhibits cholinesterase competitively. Reversible. Lasts 2–4 hours. Also has excitatory action on the neuromuscular apparatus. Massive doses cause some ganglionic blockade.
Distribution in Body	Does not penetrate epithelial or lipoid barriers. Quaternary base—does not penetrate.	Penetrates lipoid structures. Passes through epithelium.	Poorly absorbed—a quaternary base. Does not penetrate epithelial or lipoid barriers.
Action on Skeletal Muscle	Competitive displacement of curare at end-plate. Reverses the action of curare. Fasciculations in large doses. Anticholinesterase activity of minor consequence.	Causes fasciculations in large doses.	Reverses the action of curare and similar drugs. Fasciculations in large doses if used alone.
Central Effects	None. Does not penetrate into nervous tissues.	Intense increase in brain activity. E.E.G. pattern shows increased activity	None. Does not penetrate into nervous tissues.
Autonomic Effects	Action similar to parasympathetic stimulation. Antagonized by atropine.	Manifests effects of parasympathetic stimulation by permitting accumulation of acetyl choline. Antagonized by atropine.	Manifests effects of parasympathetic stimulation. Antagonized by atropine
Dose	5–10 mgm. I.V. Action transient. Recombination of displaced curare at end plate may occur. Requires repeated doses. Action not cumulative.	Physostigmine Salicylate. Dose 0.5–1.0 mgm. Generally not suitable for severe over curarization.	Neostigmine Bromide tablets 15–30 mgm. Neostigmine methyl sulphate for I.V. use. Dose 0.5–1.0 mgm.

THE PHARMACOLOGIC BEHAVIOR OF CHOLINERGIC (PARASYMPATHETIC) POSTGANGLIONIC AUTONOMIC FIBRES



ATROPINE AND RELATED DRUGS

CHEMISTRY—All are alkaloids obtained from plants of order solanacea. Structurally they are tropic acid esterified with tropine or scopine.



These alkaloids are basic in reaction in aqueous solution They form salts with the mineral acids—sulphuric, hydrobromic, and hydrochloric They are precipitated by the alkaloidal reagents. Hyoscyamine is converted to atropine by heat and alkali. Minute amounts possess marked activity They possess two actions—a central one and a peripheral. Small doses (gr 1/150) stimulate the nervous system centrally and depress the myoneural endings of the parasympathetic division of the autonomic nervous system. Larger doses stimulate first and then depress.

PARASYMPATHETIC DEPRESSANT DRUGS

Name	Chemical Name	Effect on Secretions	Effect on Cardiac Vagus	Effect on Gastro-Intestinal Tract	Effect on Eye	Central Effect
Atropine	Tropine tropate.	Effective for anesthetic use.	Effective for anesthetic use	Relaxes smooth muscle.	Causes prolonged mydriasis.	Stimulates.
Homatropine	Tropine mandelate (mandelic acid has one carbon less than tropic)	Weaker than atropine Not suitable for anesthesia.	Less pronounced than atropine.	Less than atropine	Causes less sustained effect.	Stimulates in large doses.
Novatropine	N methyl bromide of homatropine.	Weaker than homatropine.	Less than homatropine.	Is effective.	Less marked than homatropine.	Less marked than homatropine.
Eumydrine	N methyl nitrate of atropine.	Similar to atropine but less marked	Similar to atropine but less marked.	Similar to atropine but less marked	Similar to atropine but less marked	Similar to atropine but less marked.
Eucatropine	Mandelate of piperidine base.	Much less than atropine Not suitable for anesthesia.	Less than atropine	Slight	Designed for use in eye. Less intense than atropine.	Less than atropine.
Trasentine	Diphenyl acetic acid ester of diethyl amino ethyl alcohol	Slight	Slight.	Pronounced	Slight	Slight.
Syntropan	Tropate of tertiary amino propyl alcohol.	Slight	Slight	Pronounced.	Slight	Slight.
Hyoscyamine	l tropine tropate.	Similar to atropine.	Similar to atropine	Similar to atropine	Similar to atropine.	Similar to atropine.
Scopolamine	l scopine tropate	Similar to atropine.	Less than atropine	Less than atropine	Less than atropine.	Depresses cortex.

ATROPINE

HISTORY—Recognized by Vauquelin in 1800 isolated and described as an alkaloid by Brandes in 1819

Cortex—Stimulated. Motor area more reactive to electric stimulation. Toxic doses cause excitement, convulsions or delirium.

Temperature Regulating Center—Stimulated by large doses. Blush center stimulated. Skin flushed and warm.

Vasomotor Center—Slightly stimulated with therapeutic doses, resulting in slight blood pressure rise. Toxic doses depress and cause fall in pressure

Respiratory Center—Stimulated. Toxic doses depress.

Vagus Center—Stimulated. Causes slowing the heart rate which persists until peripheral effect ensues.

Medullary Centers—Stimulated. Degree depends upon dose

Carotid-aortic Chemoreceptors—No significant clinical effect.

Lungs—Respiratory rate slightly increased. Minute volume exchange increased. Tidal exchange increased. Relaxation of bronchial musculature from vagal depression. Oxygen consumption increased, carbon dioxide production increased, but total blood carbon dioxide unchanged.

Metabolism—Slightly increased

Gallbladder—Bile production unaffected duct relaxes Reduces motility

Adrenal—No change in epinephrine output.

Liver—Function not significantly changed. Carbohydrat metabolism unaffected.

Kidney—Not significantly affected by therapeutic doses

Ureters—Relaxed Movements inhibited Relieves spasm caused by morphine

Bladder—Relaxed by large doses

Blood—No significant changes bleeding and clotting time unchanged slight increase in total leukocyt count

Elimination—One therapeutic dose eliminated within 14 or 15 hours. One-third, unchanged, found in urine Remainder hydrolyzed; distributed in all tissues.

Eyes—Ends of parasympathetic nerves depressed, resulting i dilated pupil. Paralyzed ciliary muscle increase in intra-ocular tension, and decreased lacrimation also result. Action persists for several days.

Mucous Membranes—Secretions decreased. Drug absorbed from mucous surfaces.

Larynx—Laryngeal nerve depressed. Depresses vagus. Antagonizes spasm of nervous origin.

Heart—Biphasic action. Decrease in rat initially followed by increase depending upon dose. 1/100 grain gives slight decrease t first maximum preliminary decrease with 1/10 grain increase in rate due t paralysis of vagal endings. N effect on myocardium. Coronary blood flow increased.

Blood Pressure—No effect except in toxic doses.

Autonomic Nervous System—Depresses cholinergic autonomic fibres (postganglionic) Prevents muscarine effects of acetylcholine and its esters. Blocking action on ganglia in larger than clinical doses.

Stomach—Motility emptying time and acidity not affected. Volume of secretion reduced.

Intestines—Motility emptying time and secretion decreased. Large doses needed t affect this response Hypermotility reduced. Stimulated when hypomotility is present. Absorbed readily from mucous surface.

Pancreas—Secretions under vagal control diminished under hormone control, unchanged.

Uterus—No effect. Slightly relaxed with large doses.

Reflexes—Cord stimulated by large doses; Babinski positive with large toxic doses.

Skeletal Muscles—Not significantly affected

Skin—Insignificant local analgesic action.

Body Temperature—Increased due to increased metabolic rat and inhibition of sweating

ATROPINE STIMULATES CENTRALLY AND DEPRESSES AUTONOMIC NERVE ENDINGS PERIPHERALLY

PROPERTIES AND PREPARATIONS—An organic base It is a white powder composed of crystals with an acrid bitter taste It is poorly soluble in water (1 in 455) It forms salts with many acids, most important of which is the sulphate The sulphate is white odorless, granular powder inactive optically melting at 190°C. and soluble in water (1 in 0 4 at 20°C) alcohol and poorly soluble in chloroform and ether Atropine sulphate is included in the U.S P XIII

SCOPOLAMINE

HISTORY—Discovered by E. Schmidt in 1888

Cortex—Depression followed by drowsiness, and then a dreamless sleep. Hallucinations may precede sleep in some cases. Not an analgesic. Enhances hypnotic effect of morphine. Delirium follows use with pain.

Temperature Regulating Center—Not affected. Toxic doses may depress.

Vasomotor Center—Not affected. Large doses cause stimulation. Toxic doses depress.

Respiratory Center—Slightly stimulated. No depression. May antagonize depression of morphine. Toxic doses depress.

Vagus Center—Stimulated. May cause slowing of pulse.

Vomiting Center—Depressed. May overcome nausea and emesis of central origin.

Vagus—Depressed at nerve endings. Action weaker than that of atropine.

Lungs—Tidal volume reduced, rate increased, minute volume exchange increased. Bronchi relaxed.

Metabolism—Slightly reduced or no change.

Adrenal—No known significant change.

Gallbladder—Bile production unaffected. Smooth muscle or motility reduced. May relieve spasm.

Liver—No significant effect. Response similar to atropine.

Kidney—No significant effect.

Ureters—Relieves spasm similarly to atropine.

Body Temperature—No significant change.

Autonomic Nervous System—Depresses autonomic cholinergic nerve fibres.

Eye—Pupils dilate. Also causes loss of accommodation. Intra-ocular tension reduced. Qualitatively responses are same as atropine but quantitatively less intense.

Larynx—Vagal reflexes inhibited. Antagonizes spasm of nervous origin.

Salivary Glands—Depressed, more actively than by atropine. Action of shorter duration.

Mucous Glands—Secretions decreased. Drug readily absorbed from mucous surface.

Heart—Pulse unchanged or slowed. Toxic doses depress rate. No effect on myocardium.

Blood Pressure—No significant change. Toxic doses may depress.

Gastrointestinal System—Motility, emptying time and secretions reduced.

Pancreas—Secretions diminished.

Uterus—Stimulates contractions and raises tone. Large doses depress.

Muscles—Not significantly affected.

Skin—No flushing or rash. Sweating inhibited.

Blood—No significant change.

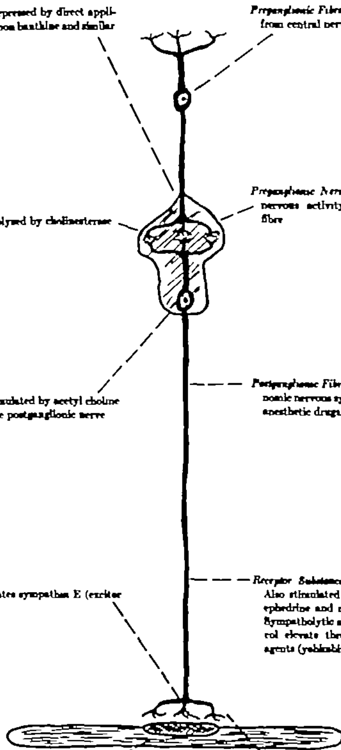
Reflexes—Superficial and deep reflexes remain active. No significant change.

Elimination—Partly hydrolyzed by tissues.

SCOPOLAMINE POSSESSES TWO IMPORTANT ACTIONS, A CENTRAL (OR CORTICAL DEPRESSANT ONE) AND A PERIPHERAL AUTONOMIC ONE (PARASYMPATHETIC DEPRESSANT)

PROPERTIES AND PREPARATIONS—An organic base existing as an almost colorless, syrupy liquid. It crystallizes from an ether solution into a white powder which melts at 59°C. It is slightly soluble in water but soluble in alcohol, chloroform and ether. It forms salts with many mineral and organic acids, most important of which is the hydrobromide which is included in the U.S.P. XIII. The hydrobromide, a white crystalline powder, is bitter and slightly efflorescent and dissolves in water (1 in 5), alcohol (1 in 20), but is insoluble in chloroform and ether.

THE PHARMACOLOGIC BEHAVIOR OF ADRENERGIC (SYMPATHETIC) NERVE FIBRES



SYMPATHOMIMET…

Name	Epinephrine	Arterenol	Ephedrine	Desoxyephedrine	Neosynephrine
Synonyms	Adrenalin suprarenin	Nor epinephrine Levophed	—	Methamphetamine Methedrine	Phenylephrine
Chemical name	Levo methyl Amino catechol	Epinephrine minus methyl group on nitrogen	Has no hydroxyl groups on aromatic nucleus. Has CH_3 group on β carbon of epinephrine	Ephedrine minus OH on [illegible]	Differs from epinephrine having only one hydroxyl in meta position on phenol
Comparison to other pressor drugs	Is standard of comparison	Lacks vasodilator component of epinephrine	Longer lasting than epinephrine	5 to 10 times more potent than ephedrine	Less potent. Longer lasting than epinephrine
Isomers	Optically active	Levorotatory form used	Levo ephedrine more active than dextro or racemic	Dextro-compound is most potent and one used	Levo rotary form is used
Properties	—	Bitartrate is white salt soluble in water	White crystalline substance prepared as sulphate or hydrochloride	Hydrochloride is white crystalline substance	White crystal in H_2O
Stability	Unstable	Readily oxidized	Base decomposes. Hydrochloride is stable	Stable	More stable than [illegible]
Source	Medulla of adrenal gland	Epinephrine from adrenal medulla contains 18%	From Ma Huang. Also synthetically	Synthetic	Synthetic
Detoxification	Destroyed by oxidation	Oxidized rapidly by enzymatic action	Slowly destroyed in blood	Slowly destroyed or eliminated	Oxidized
Effect on myocardium	Stimulates. Increases output	No notable stimulating effect	Stimulates. Increases output	Stimulates. Increases output	Increases output
Effect on cardiac rhythm	Increases rate. Stimulates myocardium	Increases output	Increases rate and output	Increase	Slows
Effect on arterioles	Constricts some. Dilates others	Increases peripheral resistance all over	Constricts. Causing pressor effect	Increase	Constricts
Effect on bronchi	Dilated	Dilates	Dilates	Dilates	Dilates
Effect on intestines	Inhibits	Inhibits	Inhibits	Inhibits	Inhibits
Stimulation centrally	Causes tremor, excitement	Less than epinephrine	Some central stimulating action	Possesses definite central stimulating effect	Slight stimulation or none
Effect on coronaries	Dilates	Increases flow	Dilates and increases flow	Dilates	Dilates
Effect on veins	Constricts	Constricts	Greater than that of epinephrine	Constricts	Constricts
Effect on denervated organs	Stimulates markedly	—	No effect	Same as ephedrine	—
Effect with cyclopropane	Causes ventricular fibrillation	Causes ventricular fibrillation	Causes arrhythmias of supraventricular origin	Same as ephedrine	Causes minor arrythmias
Tachyphylaxis	None	None	Present	Present	Present
Effect on systolic pressure	Elevates markedly	Elevates	Elevates	Elevates	Elevates
Effect on diastolic pressure	Lowers I.M. raises I.V.	Elevates	Slight elevation	Elevates	Elevates
Effect on pulse rate	Accelerates	Little change	Accelerates	Accelerates	Slows reflexly
Effect with ergotamine	Yes	No vasodilatation	None	Like ephedrine	Reverse
Use to prolong local anes.	Most effective of vasoconstrictors	May cause slough	Not satisfactory	Not used	Moderate effect
Use to prolong spinal anes.	Very effective	Useful	Not satisfactory	Not used	Moderate effect
Use to shrink mucous membranes	Effective	Useful	Satisfactory	May be used	[illegible]% effective
Use for allergy	Effective	Effective	Effective	Effective	Not as effective
Onset of pressor Action I.V.	Immediate. Lasts several minutes	Transient like epinephrine	Within several minutes	Within several minutes. Lasts longer than ephedrine	0.5 mg raises B.P. for 15 m[illegible]
Onset of pressor Action I.M.	Within 3–5 minutes. Lasts 5–15 minutes	Transient like epinephrine	10–20 minutes. Lasts several hours	Lasts longer than ephedrine	5 mg. raises B.P. 1–4 hrs.
Onset of pressor Action orally	Not effective	Not used	Effective. Lasts several hours	Effective. Lasts longer than ephedrine	30–40 mg raises B.P. 1–4 h[illegible]
Effect on respiration	Does not stimulate center. May cause apnea reflexly	None	Slight. Stimulating action on respiratory center	More central action than ephedrine	Slight or none
Side actions	Tremor, excitement, pallor	Same as epinephrine	Tremor, excitement. Pallor. Nausea	As vasopressor for spinal anesthesia	Slight or none
Most common uses	Vasopressor for spinal anes. Short action. Not suitable	As vasopressor	More prolonged than ephedrine	More potent and longer lasting than ephedrine	As vasopressor, nasal [illegible]
Site of action	Adrenergic. Directly on effector cells	Adrenergic. Directly on effector cells	Adrenergic. Directly on effector cells	Adrenergic. Directly on effector cells	Adrenergic. Directly on cells

DRUGS

Cobefrin	Benzedrine	Privine	Clopane	Vasoxyl	Oenethyl	Pituitrin
Corbasil	Amphetamine	Naphazoline	Cyclopentamine	Methoxamine	E A 1	Hypophamine
1 (3,4-Dihydroxy phenyl) amino propanol	Phenyl iso propylamine	2(1-Naphthyl methyl) imidazoline	Cyclopentyl-2 methyl-amino propane	Di methoxyl phenyl iso-propyl amine	6 methyl amino heptane	Contains pitocin (oxytocin) and pitressin (vasopressin)
Differs from epinephrine in being about ½ as potent	More central than peripheral acting	Peripheral acting	Same potency as ephedrine	—	Straight chain	Both are polypeptides of 8 amino acids.
—	Dextro form more active than or levo	—	—	—	None	None
White powder	Base is soluble liquid. Sulphate is white powder	Hydrochloride is white powder	Hydrochloride is white powder	Hydrochloride is white crystalline material	—	Biological product—dried gland. Also prepared synthetically
Not stable	Stable	Stable	Stable	Stable	Stable	Stable
Synthetic	Synthetic	Synthetic	Synthetic	Synthetic	Synthetic	Post. lobe of pituitary
Oxidized	Resistant to amine oxidase	—	—	—	—	Detoxified by liver
Same as epinephrine only less potent	Stimulates	Stimulates(?)	Stimulates	Does not stimulate	Stimulates	None. May reduce cardiac output (ischemia)
Like epinephrine	Some irregularities in large doses	No serious arrhythmias	No serious effect	No serious effect	Increases output	None
Constricts	Constricts	Constricts	Constricts	Constricts	Constricts	Constricts. Also constricts capillaries
Dilates	Dilates	Dilates	Dilates	Dilates	Dilates	Constricts
Inhibits	Inhibits	—	Inhibits	Inhibits	Inhibits	Constricts
Less than epinephrine	Stimulates cortex and medulla	Little or none	½ less than ephedrine	Slight or none	None or slight	None
Dilates	Dilates	—	Dilates	Dilates	Dilates	Constricts, causes ischemia
Constricts	Constricts	Constricts	Constricts	Constricts	Constricts	Constricts
—	No effect	No effect	—	—	No effect	No effect
Causes arrhythmias	Some increase in irritability	—	—	Does not cause arrhythmias	No effect	Does not sensitize heart. Not like epinephrine
Present	Present	Present	Present	Present	Present	None
Elevates	Elevates	Elevates	Elevates	Elevates	Elevates	Elevates
Elevates	Elevates	Elevates	Elevates	Elevates	Slightly	Elevates
Increases	Variable. Usually reduced	Increases	Variable	Slows. Atropine reverses	Slight increase	Slows
—	Fails to reverse	—	—	—	—	None
½ less than epinephrine	Not used	Not used	Not as effective as epinephrine	Not used	Not useful	Not suitable
Not used	Not used	Not used	Not as effective as epinephrine	Not useful	Not useful	Less effective than epinephrine
May be used	Very effective	Used extensively	½% solution effective	Not used	Useful	Not suitable
May be used	Not used	Not used	Useful	Not used	Useful	Not suitable
Within several minutes	1-5 mg. within 5 minutes	Not used	10 mg. for 10-15 min.	5-10 mg. for 30-60 min.	50-100 mg 30 min.	Immediately 15-60 min.
—	Within 3 minutes 10 mg for several hrs.	Not used	25 mg for 30 min.	10 mg. 30-60 min.	100 mg for ½ to 1 hr	5-10 min.
Not used	5-10 mg for several hrs.	Not used	Not used	Not used	Not used	Not used
Like but less than epinephrine	Distinct stimulation	None	None	Does not stimulate	None	No effect
Like epinephrine but milder	Central stimulating effect	Slight or none	Like ephedrine	Slight or none	Slight or none	Syncope from decreased output of heart
To prolong local anes.	To reverse narcosis. As an analeptic	As vasoconstrictor	As vasopressor or nasal decongestant	Vasopressor for spinal anes.	As vasopressor for spinal anes.	As vasopressor. As oxytocic 5-10 units
Adrenergic on effector cells	Adrenergic on effector cells	Adrenergic at receptor substance	Adrenergic at receptor substance	Adrenergic directly on effector cells	Adrenergic on receptor substance	On all smooth muscle
						Pitocin acts only on pregnant uterus
						Pitressin on all muscle and [illegible]

ANALEPTICS

DEFINITION—An analeptic is a drug capable of stimulating the normal central nervous system which is used to overcome depression of that system. Ordinarily the term denotes restoratives used to reverse narcosis.

BASIC MECHANISMS CAUSING ACUTE CENTRAL NERVOUS SYSTEM DEPRESSIONS

1 Disturbances in cell nutrition resulting from changes in composition of arterial blood.
  (a) Reduction in oxygen tension (anoxia) or carbon dioxide excess. Result of respiratory disease or failure
  (b) Reduction in concentration of nutritive material. Glucose is principal substance so affected.

2. Disturbances in cell nutrition resulting from circulatory failure:
  ( ) All circulatory failure characterized by low systemic blood pressure acts accordingly—heart failure, shock, loss of vasomotor tone
  (b) Local circulatory changes—cerebral arterial spasm, thrombosis, increased intracranial pressure

3. Disturbance of intracellular metabolic processes:
  ( ) Depressant action of exogenous substances—narcotic and hypnotic drugs.
  (b) Action of endogenous substances—ketones and other products of disturbed metabolism.
  (c) Disturbances of intracellular enzyme activity—deficiency diseases.

TYPES OF ANALEPTICS

1 Drugs whose value depends upon the *stimulating action* which is primarily or exclusively on *vital centers* in brain stem. Picrotoxin, coramine, metrazol act primarily on medullary centers.

2. Agents which act *reflexly to stimulate vital centers*
  (a) Carotid body stimulants—Lobelin, cyanides, nicotine act on the chemoreceptors to reflexly stimulate the medulla.
  (b) Sensory nerve stimulants. Ammonia, subcutaneous ether, camphor reflexly act on the nervous system.
  ( ) Physical agents—cold, slapping, pressure on nerves, dilatation of sphincters reflexly stimulate the nervous system.

3 Agents which *improve blood supply to brain* and restore the activity of vital centers by correcting the anemia following circulatory failure. Usually cause hypertension and tachycardia—oenethyl, pituitrin, ephedrine

4 Agents which possess *dual action* and both stimulate the vital centers and the cardiovascular system. Benzedrine and desoxyephedrine possess vasoconstrictor and central action.

5. Agents which affect *cellular metabolism* and affect respiratory enzyme action—pyruvates, succinates, fumarate and similar substrates may reverse narcosis in such a manner

POSSIBLE MODE OF ACTION OF ANALEPTICS

Exact mode of action of analeptics not settled. One or a combination of the following may explain mode and site of action:

1. May inactivate narcotic by neutralizing effect—not probable.

2. May cause decrease of concentration of narcotic in cell.

3 May increase excitability of the nerve cell. Overcomes depression.

4. May displace the narcotic from combination with dehydrogenases or may act as coenzyme. Affects respiratory enzymes.

5. May combine with neural protoplasm to overcome effect of narcotic.

CHIEF SITES OF ACTION OF ANALEPTICS

CENTRAL NERVOUS SYSTEM—Stimulants may act—(1) Selectively upon certain areas of cerebrospinal axis and ultimately stimulate all portions or (2) Act uniformly on all portions not favoring any particular portion (3) May stimulate from above downward (4) Stimulate from the cord upward Sustained intense stimulation is usually followed by depression. Not all stimulating drugs are suitable as analeptics. The suitable stimulants exert their primary action on the medullary centers.

Cortex—May be primary site of stimulation. Atropine camphor benzedrine act primarily Metrazol, picrotoxin and strychnine act secondarily after medulla has been stimulated. Overdosage causes convulsions. May be confined to only one group of muscles. Centers in cortex may be affected.

Medullary Centers—Drugs act by increasing blood flow through medulla or increasing sensitivity of cells to CO_2. Center needs O_2 to function and is further depressed by O_2 lack. Stimulating drugs of no value to depressed center without O_2. Center affected directly by picrotoxin, metrazol, coramine and atropine

Vasomotor Center—Stimulated usually after respiratory center

Spinal Cord—Stimulated in two ways

(1) Reflexly through somatic pathways. Rectal dilatation, subcutaneous ether or camphor inhalation of ammonia and irritating gases act reflexly

(2) Directly on centers by specific drugs. Strychnine morphine and picrotoxin act this way Tetanic type of convulsions may result.

Sympathetic Effector Cells—Pressor effect elicited by numerous amines. Results in improved circulation in medulla and other structures affected by epinephrine ephedrine cobefrin, etc

Peripheral Nerves—Transmission of painful stimuli, cold, pressure, etc stimulate the centers reflexly

Carotid Body—Cells respond to drugs which interfere with tissue respiration. The respiratory center is reflexly stimulated. Nicotine lobeline, cyanides and coramine exert primary action on chemoreceptor cells.

Heart—Cardiac output may be improved by dilatation of coronary vessels and subsequent increase in nutrition.

Blood Vessels—Vasoconstriction may follow stimulation of vasomotor center giving rise in blood pressure and increasing circulation.

Smooth Muscle—Stimulation causes vasoconstriction and improvement of circulation. Pituitrin and pitressin so act.

Combined Action, Muscle and Nerve Endings—Certain sympathomimetic amines act beyond as well as at effector cells, yielding pressor action. Benzedrine ephedrine and neosynephrine may so act.

Muscles—Stimulated directly by stretching. May reflexly stimulate respiration (tongue and pharyngeal muscles)

USES OF ANALEPTICS

(1) To overcome depressed states, notably those resulting from narcosis.
(2) To induce convulsions for various forms of "shock" therapy

DISADVANTAGES AND OBJECTIONS TO ANALEPTICS

(1) They do not accelerate destruction or elimination of the depressant drug

(2) A depressant action may follow stimulant action of analeptic and be superimposed upon depression from narcotic.

(3) May increase oxygen consumption of cells already depressed by coexistent anoxia.

(4) Possesses undesirable side actions.

(5) Convulsions may follow if inadvertently administered in mild depressions or in comas not due to depressant drugs.

METRAZOL (CARDIAZOL)

CHEMISTRY—Metrazol is pentamethylenetetrazol. It is formed by condensing cyclohexanone with hydrazoic acid.

PROPERTIES

White crystalline powder. M.P. 57 to 58°C. Soluble in water and most organic solvents. Aqueous solutions are neutral. Prepared in 10% aqueous solution for parenteral use. Used in tablet form (1.5 gr.) for oral use. Included in N.N.R. Stable and boils without decomposition.

Central Nervous System—Stimulates all parts of the cerebrospinal axis. Stimulates from above downward.

Cortex—Stimulated. Marked restlessness, excitement and increased motor activity followed by epileptiform convulsions. Depression follows stimulation from large doses.

Medulla—Stimulated when depressed. Onset of action and maximum effect immediate and brief.

Cerebral Vessels—Dilated.

Thalamus—Stimulated. Convulsions occur after ablation of structures above thalamus.

Respiratory Center—Stimulated if depressed. No remarkable effect on normal center except with large doses.

Cord—Stimulated by large doses. Restores depressed spinal reflexes. Increases hyperirritability resulting from strychnine and other cord stimulants.

Vasomotor Center—Stimulated by large doses administered rapidly causing an elevation of blood pressure. Suitable only in circulatory failure of central origin.

Oral Mucosa—Rapidly absorbed from this site.

Vagus Center—Stimulated. May cause bradycardia.

Heart—No stimulating effect on myocardium or conductive tissues. No effect on coronary vessels. Occasional transient premature beats.

Vomiting Center—May be stimulated causing nausea, retching and vomiting.

Blood Pressure—Transient hypotension may follow from intravenous injection due to transient vasodilatation.

Carotid Body—No remarkable effect.

Gastrointestinal Tract—Readily absorbed from the gastrointestinal tract.

Carotid Sinus—No remarkable effect.

Blood Vessels and Arterioles—No constriction. May cause dilatation of splanchnic vessels causing a transient hypotension.

Lungs—Respiratory movement stimulated in both depth and rate. Metabolism increased.

Arterioles (peripheral)—No effect. Not suitable for peripheral circulatory failure.

Elimination—Distributed equally to all tissues. Rapidly detoxified in the liver. Convulsive doses detoxified in less than one hour. None detected in urine.

Capillaries—No effect. Not suitable for peripheral circulatory failure.

DOSE

100–500 mgm. I.V.

USES

(1) As stimulant in depressed states resulting from central nervous system depressants.
(2) To induce convulsions in shock therapy.

PICROTOXIN

HISTORY—Discovered by Boullay in 1812. First prepared in crystalline form by Pelletier and Couerbe in 1834

CHEMISTRY

Classed as an amaroid (not an alkaloid). Contains no nitrogen. Structural formula undetermined. Empiric formula ($C_{30}H_{34}O_{13}$). Probably composed of equimolecular portions of picrotin ($C_{15}H_{18}O_7$) which is physiologically inactive and picrotoxinin ($C_{15}H_{16}O_6$) which is convulsant.

SYNONYMS

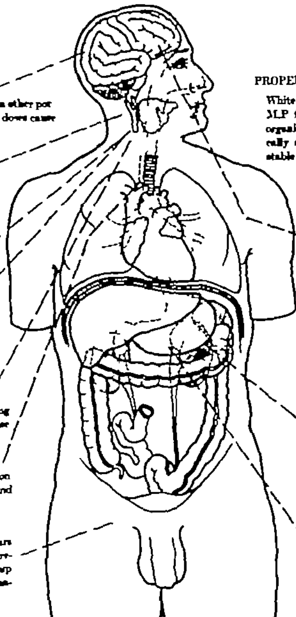
Cocculin.

PREPARATION

Extracted from the berries of Cocculus Indicus and related plants indigenous to India and East Indian Islands. Berries used for trapping fish—fish berries.

PROPERTIES

White intensely bitter lustrous, crystalline powder. M.P. 200°C. Soluble 1 in 344 water at 10°. Soluble in organic solvents and alkalis. Aqueous solution optically active. Prepared in a 0.3% solution which is stable and neutral. Included in the U.S.P. XIII.



Medulla—Stimulated more prominently than other portions of cerebrospinal axis. Subconvulsive doses cause no effect in normal subjects.

Respiratory Center—Stimulated, particularly when depressed by anesthetic drugs. Convulsive doses necessary to cause stimulation of respiration in normal subjects.

Vasomotor Center—May be stimulated, causing elevation of blood pressure. Subconvulsive doses cause no effect in normal subjects.

Vomiting Center—Stimulated. Emesis occurs frequently. Subconvulsive doses cause no effect in normal subjects.

Vagus Center—May be stimulated, causing slowing of heart. Subconvulsive doses cause no effect in normal subjects.

Cord—Affected last. Reciprocal innervation not lost. *Limbs are alternately flexed and extended.*

Excretion—Subconvulsive dose disappears from blood in 20 minutes. Traces may remain for several hours. All tissues take up drug. Detoxified in body—exact fate unknown.

Cortex—Stimulates—less so at first than mid-brain or medulla. Large doses cause *convulsions. Depression follows* stimulation if convulsion occurs. Little or no effect in normal subjects until toxic doses are given.

Absorption—From all channels—oral, subcutaneous, intramuscular and intravenous.

Stomach—May be absorbed rapidly *from mucous surfaces.*

USES

For antagonizing barbiturate depression, particularly long and intermediate acting types. Also used for overcoming certain narcosis.

ONSET OF ACTION

Latent period lasting as long as 20 minutes. Action is sustained and prolonged. (Longer than metrazol.)

DOSE

Packaged in 3 mgm. per cc. doses. Given slowly to secure desired therapeutic effect.

CONTRAINDICATIONS

Morphine poisoning. May enhance convulsions. Acute al

CORAMINE (NIKETHAMIDE)

CHEMISTRY—Coramine is the diethyl amide of nicotinic acid or pyridine β carboxylic acid Effects on respiration noted by Faust in 1926

PROPERTIES—Light viscous oily liquid, somewhat yellowish in color Very soluble in water B.P 280°C.

Cerebrospinal Axis—Stimulates in large doses only Toxic doses excite higher motor and other centers at first and then depress and cause death by respiratory failure

Cortex—Toxic doses stimulate and cause convulsions. These are followed by respiratory depression and coma.

Vasomotor Center—No direct effect. May affect it secondarily due to relief of anoxemia.

Lungs—Increases ventilation if respiratory center is affected. Duration and degree varies with type of depression.

Respiratory Center—Stimulated reflexly via the sino aortic bodies. Affects a depressed respiratory center more than normal one

Heart—No notable effect. Elevation of blood pressure may follow use of large doses due to reversal of depression of vasomotor center

Carotid and Aortic Body—Partly reflexly stimulates respiration by stimulating chemoreceptors.

Blood Volume—No significant clinical effect. Not suitable for respiratory depression due to shock. Not suitable for peripheral circulatory collapse due to blood loss, shock from trauma or collapse of neurogenic origin

Metabolism—Effective as vitamin in therapy of pellagra and other diseases due to deficiency of nicotinic acid

Muscles—Questionable increase in muscle tone with large doses. Not of clinical significance.

Elimination—No cumulative action Rapidly inactivated. Presumably liver is site of destruction.

PREPARATION

Sterile 25% aqueous solution. Coramine is proprietary name. Nikethamide is council accepted name.

DOSE

0.250 to 0.500 gm. intravenously or *intramuscularly. Doses larger than* 0.5 gm. should be administered very slowly and patient watched for signs of convulsions.

USES

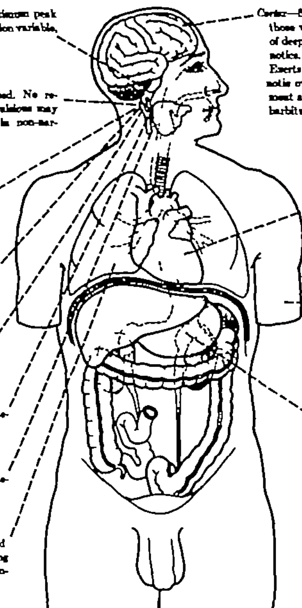
As an analeptic in management of morphine avertin or barbiturate and other types of central nervous system depression

BEMEGRIDE (MEGIMIDE)

SYNONYMS—Megimide NP 13

HISTORY—First synthesized in 1011 during investigation of series of derivatives of glutarimide for anticonvulsive properties. Allied to glutethimide (Doriden) which is an alpha substituted glutarimide Marshall and Valence found alpha substituted compounds to be anti-convulsants. Studied pharmacologically by Shaw and his colleagues (Australia) 1951

DESCRIPTION—Chemically it is beta-ethyl methyl-glutarimide White colorless compound with slightly bitter taste Crystals irregular and hexagonal. Readily soluble in alkalais, alcohol, ether acetone benzine Melts at 121°C Aqueous solutions are neutral. Stable when autoclaved at 115°C. Crystallizes if stored in a cool place Prepared in a saturated solution.



USES

As an analeptic for depressed states resulting from overdosage of barbiturates and other hypnotics. Not true barbiturate antagonist. Evidence that it acts by competitive inhibition is lacking. Useful as an adjunct to essential supportive therapy

ADMINISTRATION

Intravenously in intermittent doses of 50 mgm. every 3 to 5 minutes until muscular tone increases nd evidence of reflex activity appears. Maximum dosage varies with degree of depression. As little as 50 mgm. may be effective. As much as 600 or 700 mgm. may be required in markedly depressed states. Regression may follow massive doses of hypnotics, particularly long-acting barbiturates.

MARGIN OF SAFETY

Wider than with metrazol or picrotoxin. More effective than metrazol nikethamide picrotoxi l treatment of coma.

METHYLPHENIDATE (RITALIN)

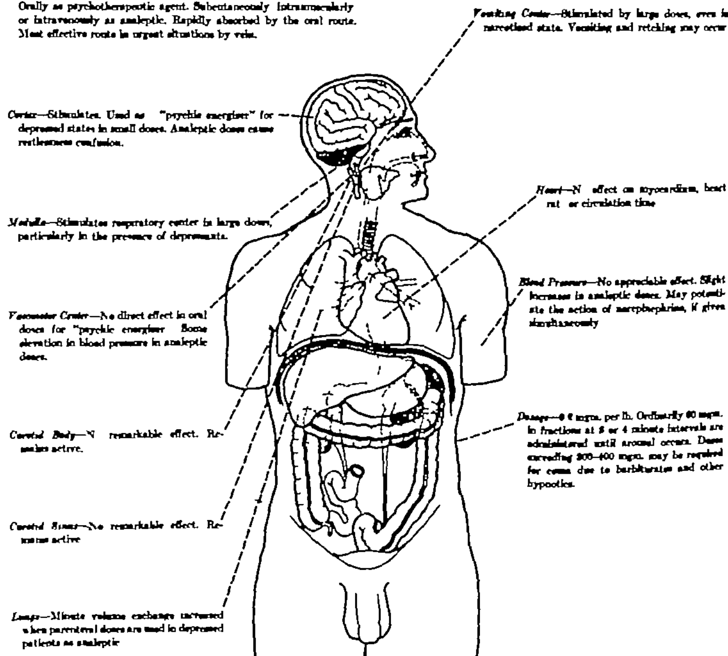
DESCRIPTION—Alpha phenyl 2-piperidineacetate hydrochloride

USES

1. To alleviate drowsiness associated with antihistaminics and tranquilizers.
2. As an analeptic to overcome depression from hypnotics
3. As psychic energizer in depressed states (psychotherapeutic agent)

ADMINISTRATION

Orally as psychotherapeutic agent. Subcutaneously, intramuscularly or intravenously as analeptic. Rapidly absorbed by the oral route. Most effective route in urgent situations by vein.



ANALEPTICS OF LESSER IMPORTANCE

Name	Camphor	Caffeine	Strychnine $C_{21}H_{22}N_2O_2$	Alpha-lobeline	Sodium Succinate	Amiphenazole
Synonym	d. camphor Japanese camphor			Lobeline		Daptazole
Chemistry	Naturally-occurring or synthetic from terpenes. A cyclic ketone. Not related chemically to metrazol.	1,3,7 methyl xanthine. A methyl purine obtained from natural sources.	Alkaloid obtained from dried seed of strychnos nux vomica. [illegible] alkaloid is used.	A derivative of pyridine. Obtained from Lobelia leaves—"Lobelia inflata" which contains three alkaloids, lobeline, b-lobeline, and lobelidone. Alpha is active.	Synthetic.	2,4-diamino 5, phenyl thiazole. Synthetic. Forms hydrochloride salt. White, dry powder. Stable. Soluble in water. Solutions decompose slowly on standing.
Properties	Amorphous white substance. Poorly soluble in water. Soluble in organic solvents.	Salts form; citrate for oral use. Caffeine sodio benzoate, 1:4 solution, for injection.	Basic compound. Forms salts. Sulphate—77% alkaloid. Nitrate—84% alkaloid. Salts soluble in water	White powder. Melting point, 130°C. Levorotatory. Forms hydrochlorides and sulphates which are used clinically	White powder soluble in water	Discard after 24 hours. Stable one week with refrigeration.
Elimination	Conjugated with glycuronic acid in liver and excreted into urine.	Diuretic. Eliminated by demethylation. Some destroyed in body; some eliminated unchanged.	Destroyed by liver (oxidized?). Small amount found in urine up to five days.		Metabolized in body	
Primary Site of Action	Slightly stimulating to cerebrum and medulla. Stimulates reflexly in subcutaneous injections. Convulsant in large doses.	Cortex primarily. Large doses medulla, still larger doses spinal cord. Used subcutaneously, intramuscularly or rectally in form of warm coffee	Spinal cord primarily. Medulla after cord. Ascending stimulation.	Medulla to slight extent. Carotid body principally. Transient action. May initiate gasp. Large doses depress the central nervous system.	Activates path of intracellular oxidation not depressed by narcotics so that cell utilizes succinate instead of glucose.	Medulla. Large doses act as convulsant. Not narcotic or barbiturate antagonist.
Effects on Circulation	No effects. Dilates coronary vessels. May affect blood pressure.	No effect on human heart. Blood pressure may rise secondarily to central effect.	No effect directly. Of no benefit.	Excites, then depresses ganglia. Has vagal excitation action. Bradycardia. No beneficial effect. Does not stimulate the heart or elevate blood pressure.	None	No remarkable effects. Not cardiac stimulant or vasopressor
Effects on Respiration	No effect. Large doses may stimulate. Usually convulsants occur beforehand.	May cause some increase. Not of benefit in marked depression.	No effect. Dose which stimulates respiration must approximate the convulsant dose.	Minute volume exchange increased during interval of gasp. May cause bronchoconstriction.	No remarkable effects. Results disappointing.	Stimulates. Increases minute volume exchange by central stimulation.
Metabolism	No effect. Convulsant doses stimulate.	Slight increase in metabolism.	Increases by the convulsive action.	Increased by large doses.	None	Increased due to stimulation.
Other Central Effects	Stimulates from above downward. Large doses cause coma. Convulsive doses stimulate medulla. Poorly absorbed.	Large doses may affect medulla. Mostly cortical stimulant.	Large doses possess curare-like action. Convulsions prevail.	Action is on chemoreceptor of carotid body. Usefulness limited to initiation of gasp in the new born.	None	
Dose	0.2 gm. I.M.	0.5–1 gm.		10–20 mgm. I.V.	4–8 gm. I.V.	
Remarks	Action variable. Not suitable as analeptic.	Action mild. Used to overcome "hangover" effects of hypnotics.	No tolerance develops. Of little benefit as analeptic.	Effective orally. Same general actions as nicotine only less potent.	Of doubtful value. Used to reverse barbiturate narcosis.	

XIII. INORGANIC GASES USED IN CONJUNCTION WITH ANESTHESIA

GASES AND VAPORS

Molecular Composition—Molecules of gases are composed of atoms. Some gaseous elements are monatomic (He—helium). Many are diatomic (N_2—nitrogen, O_2—oxygen, H_2—hydrogen, Cl_2—chlorine, Br—bromine) and others are triatomic (O_3—ozone). Non-elemental gases may be diatomic (NO—nitric oxide), tri (N_2O—nitrous oxide), tetra (NH_3—ammonia), penta (N_2O_3—nitrogen trioxide), etc.

Pressure—All gases exert pressure. Pressure is the force exerted by bombardment of the walls of a confining space by molecules. Force is exerted by rapid motion of molecules on side of containing space. Molecules tend to distribute themselves evenly in a given space (diffusion). *Tension* (used in physiology) and *pressure* are synonymous.

Boyle's Law—The volume of a gas varies inversely as the pressure provided the temperature remains constant. Doubling the pressure halves the volume. Quadrupling the pressure reduces the volume to one-fourth. Reducing the pressure to one-half doubles the volume; to one-fourth quadruples the volume. Example: 100 cc. of a gas at 20° and 80 mm. Hg will have a volume of 20 cc. at 400 mm. Hg. pressure.

Charles' Law—The volume of a gas varies in direct proportion to its absolute temperature if pressure remains constant. Volume increases 1/273 of its volume for each degree it is warmed above 0°C. and shrinks 1/273 of its volume for each degree it is cooled below 0°C. Example: A gas having a volume of 1 liter at 0°C. will have a volume of 2 liters at 273°C. provided pressure remains constant.

Dalton's Law—In a mixture of gases the pressure exerted by each gas is independent of the others and acts as though alone. The sum of the pressure of each equals total pressure. Example: In a mixture of 25% cyclopropane, 25% oxygen and 50% nitrogen having total pressure of 80 cm. Hg O_2 exerts a pressure of 20 cm. Hg—cyclopropane 20 and nitrogen 40.

Henry's Law—The amount of a non-reacting gas which dissolves in liquid is directly proportional to the partial pressure of the gas provided the temperature remains constant. Solubility of gas decreases as the temperature rises or as the concentration of inorganic ions increases in the liquid. Example: If 1 gram of gas dissolves in a given volume of a liquid at 0°C. and 1 atmosphere, 2 grams will dissolve at 2 atmospheres, 4 grams at 4 atmospheres and ½ gram at ½ atmosphere. The volume is independent of the pressure and remains constant for a given temperature.

Graham's Law—The rate of diffusion of one gas compared to another varies inversely as the square roots of their molecular weights. Example: Oxygen is 16 times heavier than hydrogen. It diffuses $1/\sqrt{16}$ or ¼ times as fast as hydrogen.

Avogadro's Law—Equal volumes of gases, even though dissimilar, at standard conditions contain same number of molecules. One gram molecule of a gas or vapor equals 22.4 liters at standard conditions and contains 6.06×10^{23} molecules (Avogadro's number). The weight of dissimilar gases varies.

Solubility Coefficient—Ostwald's—The volume of gas absorbed by a unit volume of liquid at conditions of experiment. Bunsen's—Volume of gas absorbed by unit volume of liquid at 0°C. and 76.0 cm. Hg. pressure.

Critical Temperature—Temperature to which a gas must be cooled to be liquefied by pressure.

Critical Pressure—The minimum pressure required to liquefy gas as it is cooled (at critical temperature).

Standard Conditions—The volume of a gas expressed at 76.0 cm. Hg pressure 0°C 29.9" Hg., or at 1033 gm. per sq. cm. or at 14.7 lbs. sq. in. at 0°C. or 32°F.

Vapor Pressure—The pressure exerted by molecules escaping from liquid. When vapor pressure equals atmospheric pressure the liquid is at boiling point.

Absolute Humidity—Number of grams of water vapor per unit volume of gas at given temperature when there is complete saturation.

Relative Humidity—The amount of water vapor actually present in given volume of gas divided by the amount necessary for saturation at a given temperature times 100, expressed per cent. Example: 100 cubic meters of gas hold 0.5 gm. of water vapor but can hold 1.0 gm. The per cent saturation is $(0.5/1) \times 100$ or 50%.

OXYGEN

HISTORY—First prepared by Stephen Hales in 1727 who did not recognize it as an element. Discovered by Priestley in 1771 also prepared by Scheele in 1771

PREPARATION

1. By the fractional distillation of liquid air Nitrogen boils off first oxygen remains as a liquid (most common method)
2. By heating BaO_2 (barium peroxide) At 800°C forms BaO and O_2. At 500°C., red heat. BaO recombines with oxygen which is admitted into the furnace as air Process is repeated



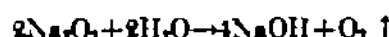
$$2BaO_2 \rightleftarrows 2BaO + O_2$$

3. Electrolysis of water



$$2H_2O \rightarrow 2H_2 \uparrow + O_2$$

4. By reacting water and sodium peroxide (oxone generator)



$$2Na_2O_2 + 2H_2O \rightarrow 4NaOH + O_2 \uparrow$$

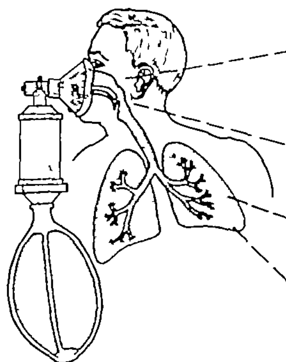


PROPERTIES

Clear colorless, odorless gas. Molecular weight 32. Solubility 4.9 vols. in 100 cc. H_2O at 0°C. and 760 mm. Hg.; 3 1 cc. at 20°C.; 2.4 at 37°C. Specific gravity 1 105 (air equals 1) Liquefies at −119°C. at 50 atmospheres pressure; boils at −183°C.; solidifies at −218°C. Electric sparks convert it to ozone (O_3) Included in U.S.P. XIII. Sold as compressed gas in metal cylinders. Usually packaged at 2000 lbs. pressure Standard color of cylinder green. Viscosity of gas at 20°C. 0 020 (water = 1)

CONTENT IN BLOOD

Released from hemoglobin by oxidizing agents (nitrites, ferricyanide) with formation of methemoglobin used in analytical methods. Approximately 19 5 cc. O_2 may be released from 100 cc blood normally



Effect on Membranes—Pure oxygen is an irritant if inhaled for period of 36 to 48 hours continuously causing pulmonary edema. Nasopharynx in animals irritated with 75% or more Questionable decrease in secretions and increase in viscosity

Effect on Cells—Oxygen under pressure suppresses respiratory enzyme giving rise to oxygen poisoning.

Diffusion—Diffuses from isolated lobe of lung rapidly Rapid absorption may be factor in atelectasis in anesthesia with rich O_2 mixture

Effect of 100% O_2—Inhalation of pure oxygen increases dissolved blood oxygen four times. Has little effect on hemoglobin carried oxygen if no anoxemia exists. No increase in ventilation follows inhalation in non-anoxic subjects.

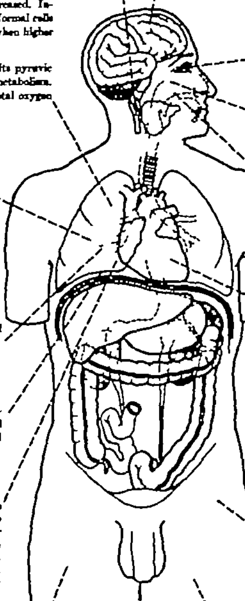
REACTIVITY

Supports combustion. Combines with hemoglobin to give oxyhemoglobin One gram of hemoglobin combines with 1.34 cc O_2

INFLAMMABILITY

Forms explosive mixtures with oil and grease under high pressure in dispensing equipment. Will cause no reaction with non-oxidizable substances.

INHALATION OF 100% OXYGEN



Carotid Body—Normal tonic control diminished. Apnea, referred to as "oxygen apnea," results when 100% oxygen is given in acute anoxia (or a drug). Respiration is being maintained by the chemoreceptors by stimulus of anoxia. Removal of stimulus leaves center inactive. Apnea does not follow chronic anoxia when vagal reflexes are active and are *maintaining respiratory drive.*

Metabolism—Oxygen consumption not increased. Increased tension of no particular benefit. Normal cells do not utilize more oxygen than normal when higher tensions are inhaled.

At increased pressure 100% oxygen inhibits pyruvic oxidase and interferes with carbohydrate metabolism. Succinoxidase activity partly reduced. Total oxygen uptake of tissues decreased.

Lungs—After 2 minutes slightly depressed due to abolition of tonic chemoreceptor activity. Stimulation follows. M.V.E. increased 8% after 6-8 minutes. Pulmonary capillaries dilated. Irritant to lower respiratory passages. Substernal discomfort follows continued inhalation of high oxygen tensions (over 280 mm. Hg).

Vital Capacity—Decreased after prolonged inhalation. Due to alterations in blood flow and pulmonary vasodilatation.

Pulmonary Vessels—Dilated by hyperoxygenation. Pressure increased. Constricted by anoxia; pressure decreased. Not related to changes in systemic pressure.

CO_2 Transport—May interfere with CO_2 transport. Oxygen from plasma used up first. Less reduced hemoglobin available for CO_2 transport. At atmospheric pressure CO_2 elimination adequate. At 2.5 atmospheres body oxygen requirement is supplied by oxygen in plasma. No reduced hemoglobin available for CO_2 transport.

Brain—No cortical effects. E.E.G. unchanged. Cerebral vessels constricted. Cerebral blood flow decreased as much as 10%.

Confusion and disorientation follows relief of chronic anoxia due to CO_2 retention with subsequent toxicity due to acidosis. 100% O_2 under increased pressure, within few minutes, causes nausea, vertigo, apprehension, depression leading to convulsions, epileptiform in character. Believed to be due to (1) inactivation of respiratory enzymes, (2) CO_2 retention.

Eyes—Retinal vessels constricted.

Ear—Eustachian tube obstructed after filling with 100% oxygen, is followed by absorption of gas and retraction of drum.

Sinuses—Obstruction after filling with 100% oxygen results in "vacuum headache" as O_2 is absorbed.

Heart—Decrease in pulse rate within 1-2 minutes of 3 or 4 beats per minute. Probably due to loss of chemoreceptor tone. Cardiac output reduced 10-12%. Stroke volume decreased. Coronary blood flow decreased up to 10%.

Blood Pressure—Slight increase in diastolic, no change in systolic. Due to increased peripheral resistance.

Systemic Arterioles and Capillaries—Generalized vasoconstriction.

Blood Concentration—Saturation increased from 97.5 to 100%. Adds 0.3 volume % to hemoglobin transported oxygen. 1.7 vols % added to 0.3% dissolved, raising total to 2 vols %. Normally venous blood has 40 mm Hg oxygen tension and 75% saturation. 100% oxygen increases it to 60 mm. Hg and 85% saturation. Arterial O_2 tension raised from 103 mm to 600 mm after 2 to 3 minutes. Pressure gradient for O_2 from blood to tissues markedly increased.

Blood—No apparent change in red blood count. Prolonged administration for several days suppresses formation of erythrocytes. Manifested by decrease of reticulocytes and not mature R.B.C. Red blood count not decreased due to long life of red cell. Newly formed (tagged with radioactive Fe) cells increase in number in circulating blood.

CARBON DIOXIDE

Carbon dioxide is an inorganic gas of extreme stability formed by the complete oxidation of carbon

HISTORY—Isolated by Black in 1757

PROPERTIES—Colorless gas, possessing pungent odor and taste M.W. 44 specific gravity 1.54 (air equals 1) Liquefies at 30.9°C. at 77 atmospheres 50 atmospheres are necessary at 20° Liquid is colorless boils at −59°C. solidifies at −78°C. to −79°C.

PREPARATION

(1) By the oxidation of coke and subsequent absorption of the gas by alkalis.
(2) By heating alkaline earth carbonates. $CaCO_3 \rightarrow CaO + CO_2 \uparrow$
(3) As a by product from fermentation of sugars.

Stability—Highly stable (decomposes at 2000°C.) does not burn; acts as diluent for O_2 in inflammable mixtures because it possesses a high capacity for heat. Absorbed by alkalis Ba or Ca hydroxides give white precipitate Present in atmosphere—.03%. Ionization in atmosphere may help dissipate electrical charges. Available as liquid in steel cylinders. Labeled grey 5 to 7½ or 10% with oxygen—grey green. Included in U.S.P XIII. Liquefies under pressure at room temperatures. Viscosity of gas at 20°C. 0.016 (water = 1)

Solubility—105 cc. CO_2 dissolves in 100 cc. H_2O at 20°C. 5.45 dissolves per 100 cc. at 37.5°C. Combines with water to form carbonic acid. Does not follow Henry law



USES

1. For shock therapy for mental diseases.
2. To facilitate breakdown of carbon monoxide hemoglobin in CO poisoning.
3. To stimulate respiration (5 to 10% in pure O_2) in depressed states and post-operatively
4. As a quenching agent to reduce range of inflammability of explosive mixtures.
5. As an anesthetic in experimental animals.
6. To fluidify secretions in diseases of respiratory tract.

DIFFUSION

Diffuses from isolated lung lobule with occluded bronchus in 6 minutes (air in 16 hours) Locally irritates skin.

PHYSIOLOGICAL AND TOXIC EFFECTS

DEFINITION OF TERMS

Hypercapnia—Increase in carbon dioxide tension of blood.

Hypocapnia—Reduction in carbon dioxide tension of blood below amount necessary to stimulate respiration.

Acarbia—Reduction of blood carbonates below accepted value

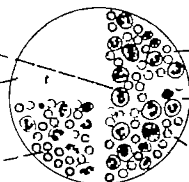
Acapnia—Reduction of carbon dioxide blood tension below level sufficient to stimulate respiratory center

BLOOD

Red Cells—Increased in number in hypercapnia. No change in hypocapnia

Oxygen Content—Favors dissociation of oxyhemoglobin.

Oxygen Capacity—Unchanged.



Clotting Time—Shortened remarkably in hypercapnia. No change in acapnia.

Glucose—Elevated. Due to glycogenolysis.

Viscosity—Increased in hypercapnia. No change in acapnia.

Vessels—Pial vessels dilated, cerebral blood flow increased. Headache results after two hours of breathing 6% mixture.

Intracranial Pressure—Markedly elevated by concentrations over 5%.

Vagus Center—Stimulated by high concentration (after vasomotor center).

Vasomotor Center—Stimulated at first. Concentrations above 20% depress, causing fall in blood pressure. Blood pressure rise persists under inhalation anesthesia.

Vomiting Center—None.

Respiratory Center—Diffuses readily into and stimulates center. Depressant drugs raise threshold to it so that it is unaffected in drug overdosage.

Carotid Body—Stimulated by tensions above those which stimulate respiratory center; therefore influences respiration little at this point.

Lungs—Increase in alveoli of 0.1% doubles ventilation; decrease of 0.1% causes apnea. 1 to 2% in inspired air increases tidal volume. 3 to 4% increases rate as well as tidal volume. 6.0% to 10.0% air increases ventilation 203% to 297%. 10.4% causes decrease in ventilation to 183% and severe dyspnea; with higher concentrations unconsciousness supervenes.

Bronchi—Constricted by low concentration, dilated by high.

Metabolism—Output 200 cc. per minute average. Varies with metabolic rate. Concentration of various parts—pharynx 2% to 6%, lips 2.5% to 4.0%—with mask on subject during anesthesia.

Diaphragm—Stimulation of phrenic nerves via respiratory center increases ventilation.

Liver—Glycogen mobilized during hypercapnia. Hyperglycemia results.

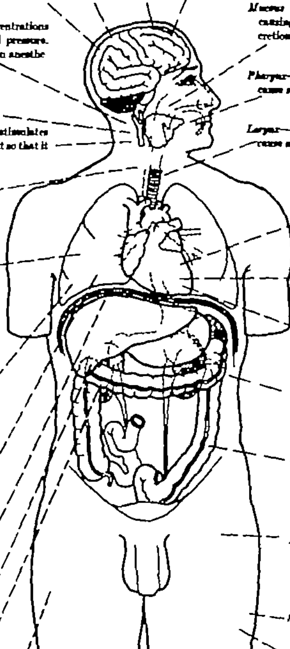
Kidney—Carbonated waters may promote diuresis.

Cortex—No effect until large concentrations are inhaled. Slight stimulation followed by depression causes narcotic effect. Small animals anesthetized with 30% or more (with O_2); 30% to 40% anesthetized dogs in 1 minute. Reflexes disappear; muscles relax, twitching. Convulsions occur in man after 10 to 15 minutes. Anesthesia may be prolonged for two hours in animals. Acapnia causes dullness and mental apathy.

Mucous Membrane—Irritated by low concentrations causing pungent sensation. Stimulation of watery secretions from mucous glands (20%).

Pharynx—No effect ordinarily. Large concentrations cause spasm.

Larynx—No effect ordinarily. Large concentrations cause spasm.



Heart—Cardiac output increased by moderate amounts—6% or more. Junctional tissues increase in sensitivity if pH is lowered, resulting in arrhythmias. Little affected by acapnia.

Venous Pressure—Increased due to dilatation of peripheral vessels.

Blood Pressure—Elevated. Falls, sometimes to below base level, when gas is withdrawn.

Blood Vessels—May constrict. Peripheral vessels dilate. Diastolic pressure may fall due to decreased peripheral resistance.

Gastrointestinal Tract—Hyperemia of mucosa facilitates absorption. Increases secretion of gastric juices. Some gas absorbed from mucous membrane.

Muscles—No effect ordinarily. May influence maintenance of tone. Tone decreased in hypocapnia. Relaxed when anesthesia is induced.

Skin—Mild irritant to skin. Skin vessels dilated. Temperature rises.

Chronic Toxicity—None.

Acapnia During Anesthesia—Hyperventilation, 10 to 15 minutes, changes pH from 7.35 to 7.70; CO_2 tension from 48 mm. to 9 mm.; total CO_2 halved; heart unchanged; blood pressure dropped 20 to 30 mm. systole and 10 to 20 mm. diastole; apnea 6 to 10 minutes after; no shock; recovery complete; hypotension not progressive; returns to normal during ventilation.

Hypercapnia During Anesthesia—Respiratory rate increased, followed by depression; blood pressure elevated as in non-narcotized subject. Pulse slightly altered; further addition of CO_2 to depression does not alter respiratory rate.

HELIUM AND RARE GASES

HISTORY—Belongs to a group of chemically inert gases known as the rare gases. Noted in the spectrum of the sun by Lockyer and Eden in 1867. Isolated in 1895 by Ramsay. Occurs in the atmosphere 1 part to 85,000. Chief world source is natural gas of oil wells of southwest U. S. which contain up to 2% of element. Separated from other gases by compression. All other gases liquefy before the helium. Clinical use reported by Barach in 1936 in New York.

PROPERTIES

Colorless, tasteless, odorless gas. The second lightest gas known. Molecular weight and atomic weight, 4.0. Specific gravity 0.1785 (air equals 1). An inert, monoatomic element. Valence 0. Liquefies at −267° C. at 2.26 atmospheres pressure; solidifies at −272°C., boils at −268.9°C. Not absorbed by activated charcoal even at low temperatures. Diffuses through some solids including glass. Possesses a high rate of heat conductivity. Viscosity at 20° 0.019 (water = 1).

Specific gravity of mixtures as follows
79% He—21% O_2—.341 (air equals 1)
60% He—25% O_2—15% C_3H_6—.538 (air equals 1)

Depressant Action—Obeys Overton-Meyer law. Possesses low oil ratio. Causes no depression at atmospheric pressure. No depressant effect under increased pressure in diving bells. (Nitrogen does.)

Effect on Membranes—None. May cause nasal tone to voice due to lightness and effect on sound waves. No effect on secretions.

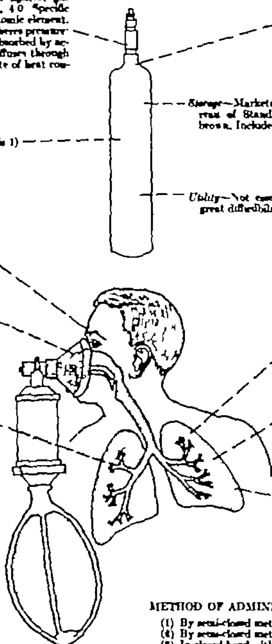
Toxicity—Physiologically as well as chemically inert. Undergoes no change in tissues. Combines with nothing. Exists in simple solution in cells and body fluids. Displaces nitrogen in tissues and body fluids when inhaled over a period of hours. Causes death by anoxia if insufficient oxygen is inhaled.

Solubility—In H_2O, at 0°C., 0.9 vols. %—most insoluble of gases.

In H_2O, 0.87 at 37°C.
In oil, 1.48 at 37°C.
Oil-water ratio, 1.7

Storage—Marketed as a compressed gas in steel cylinders. Bureau of Standards color—brown; with oxygen, green and brown. Included in the U.S.P. XIII.

Utility—Not essential to life. Used because of lightness and great diffusibility. Decreases resistance to breathing.



Elimination—Not altered in body. Minute amounts pass through skin. Mostly eliminated through lungs. Desaturation slow—requires several hours, if tissues have been saturated.

Absorption—Complete body saturation requires 5 to 7 hrs. Diffuses slowly from isolated lobule of lung with circulation intact (26 hours; air in 16 hours).

Effect on Ventilation—Lightens respiratory load and decreases effort in breathing.

USES

(1) To facilitate respiratory exchange in acute and chronic obstructions of respiratory tract (asthma, tracheal stenosis, etc.)
(2) As a quenching agent for reducing range of explosiveness of anesthetic mixtures.
(3) As a diluent to replace nitrogen of air for deep sea diving.
(4) As a contrast medium instead of air in encephalography and similar procedures.
(5) As a diluent for oxygen in inhalation methods (to avoid high oxygen concentrations).

METHOD OF ADMINISTRATION

(1) By semi-closed method continuous (expensive and wasteful)
(2) By semi-closed method followed by closed system.
(3) In closed hood with rebreathing.

OTHER RARE GASES—Neon, argon, xenon, krypton are also inactive and inert elements. Argon behaves like nitrogen when inhaled under pressure and causes nervous system depression. It possesses a higher oil-water ratio than helium. Oil/water ratio 5.32. Other gases have not been used clinically. The rare gases are inert and possess no valence. None are essential to life. Surgical anesthesia has been produced by the inhalation of xenon.

NITROGEN

HISTORY—Nitrogen is an inert diatomic element which combines with other elements with difficulty. First isolated by Rutherford in 1772.

PREPARATION

1. By the fractional distillation of liquid air as a by-product in the manufacture of oxygen.
2. By heating ammonium nitrite in air (laboratory method) $NH_4NO_2 + Heat \rightarrow N_2 + 2H_2O$
3. By absorbing oxygen from air by suitable chemical. Residual gas is nitrogen.

PROPERTIES

Colorless, inert, tasteless gas. Molecular weight 28, specific gravity 0.967 (air equals 1). Solubility 2.4 cc. at 0°C. and 76 cm. *Hg. 1.28 vols. % dissolve in H_2O at 37°C.; 6.67 vols. %* in oil. Oil/water ratio 5.24. Liquefies at −140°C. at 75 atmospheres pressure. Solidifies at −214°C. Boils at −196°C. Does not combine with water or other substances. Aided by high pressure and electricity it forms oxides, NH_3, etc. Does not support combustion. Dispensed as a compressed gas in steel cylinders. *Critical temperature below room temperature.* Possesses a high heat capacity and is, therefore, an effective quenching agent. Viscosity of gas at 20°C. 0.017 (water = 1)



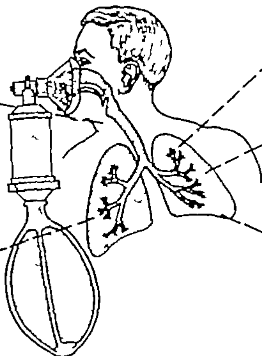
USES

(1) *As diluent to reduce high oxygen tensions during inhalation anesthesia.*
(2) As quenching agent in anesthetic mixtures to reduce range of inflammability.
(3) To induce anoxemia for diagnostic purposes (cardiac disease) or therapeutic purposes (shock therapy in mental diseases).

Diffusion—Elimination from tissues follows physical and chemical laws pertaining to other inert gases. Passes from isolated lung lobule with blood supply intact in 18 hours (air requires 10).

EFFECT ON TISSUES

No known effect. Causes death from anoxia if administered pure.



Alveolar Concentration—Tension in mm. Hg: 573 alveolar; 596 inspired, 570 expired.

NARCOTIC ACTION

Obeys Overton-Meyer Law. Non-narcotic action ordinarily. Possesses narcotic properties when administered at several atmospheres pressure. Causes central nervous system depression in divers. Rapid decompression causes appearance of bubbles in tissues and syndrome known as "the bends."

Distribution in Tissues—Does not combine in body. Exists in simple solution in plasma inter and intra cellular liquid. Arterial and venous blood concentration identical. Dissolved in all tissues and body fluids. Found in hollow viscera such as pleura, intestines. Displaced slowly by oxygen or helium using semiclosed apparatus. Six to seven hours required for almost complete desaturation.

XENON

HISTORY—Discovered by Ramsay and Travers (1898) in liquid air. Lawrence (1946) suggested from work in rats and oil/water ratio that Xenon should have anesthetic properties. Introduced as an anesthetic agent in animals and man by Cullen and Gross in 1952 (Iowa). Pittinger and co-workers studied pharmacologic properties.

PROPERTIES—Rarest and heaviest of the rare gases. Xenon (Xe) is a colorless, odorless, tasteless non-irritating inorganic gas. Present in the atmosphere in a ratio of 1 to 20 million of air. Obtained as a by-product of the fractional distillation of liquid air. Inert. Forms no stable compounds with other elements. M.W. 131.3 A.W. 131.3 B.P. −107.1°C. M.P. −112°C. Density 5 gm per liter. Critical temperature 14.8°C at 57 atmospheres. Slightly more viscous than air.

Absorption Coefficient—1.7 in oil at 37° and .085 at 37° in water. Oil/water ratio 20.

Electroencephalogram—Difficult to differentiate definite levels. Patterns consisting of burst suppression and total suppression not seen, even at maximal concentrations. Frequency is slowed but is more rapid than that noted with ether or cyclopropane. Does not produce very slow single rhythmic pattern of type seen with ether. Change is not as marked or dramatic as those described for other agents.

Brain Oxidation—80-20 mixture does not inhibit guinea pig brain tissue oxidation.

Medullary Centers—No apparent depression or stimulation.

Lung—Respiration not altered appreciably. Ventilation adequate. Not irritating.

Kidney—Urea clearance unchanged.

Blood—Hemoglobin content, red and white cell, hematocrit per cent, sedimentation rate, bleeding and clotting time unchanged. Relative increase in the number of segmental cells.

Creatinine, non-protein nitrogen, phosphorus, potassium, sodium, urea nitrogen unchanged. Glucose slightly decreased. Slight increase in platelets. No increase in sugar. Slight decrease in serum potassium. Relative bradycardia.

Flammability—Completely inert, non-explosive. Molecule has no binding force.

Uses—As research tool only. Expensive and scarce.

Concentration—80%-60%. Yield anesthesia lower 1st plane upper 2nd plane.

Potency—Comparable to that of ethylene.

Eyes—Lid reflex disappears. Corneal reflex active.

Roving eyeballs. Pupils constricted. Lid reflex absent.

Salivary Glands—No mucous formation.

Pharynx—Reflex obtunded. Airway tolerated during anesthesia.

Larynx—No spasm, no irritation, no mucous formation.

Heart—Relative bradycardia occurs. Blood pressure remains unchanged. Arrhythmias absent.

Muscles—Sufficient relaxation of jaw muscles to insert airway. Neuromuscular activity (twitchings and convulsions) absent.

Distribution in Tissues—If quantity in brain = 100% radioactive Xenon is distributed as follows in other tissues: Adrenal gland 188%; liver and spleen 58%; striated muscle 65%; perirenal fat 100%, heart and thyroid 80%; skin 21%, fat depots 25%. Bone, urine—traces. Stable in body. Eliminated by exhalation.

ADMINISTRATION

Semi-closed system during induction; closed for maintenance.

(a) Consciousness—Lost at 80% inhaled concentration.
(b) Induction—Rapid, mild without excitement.
( ) Recovery—Rapid—within 5 minutes. No excitement. Sensorium clear.

SECTION XIV SOME CLINICAL CONSIDERATIONS

PRE-ANESTHETIC MEDICATION

Reasons for administering premedication and drugs used are as follows

(1) For psychic sedation—barbiturates, opium alkaloids, avertin.
(2) To obtain an additive or synergistic effect—(opium alkaloids, demerol, procaine, methadon) between drugs and contemplated anesthetic agents.
(3) To reduce reflex irritability and metabolic rate—opium alkaloids, avertin.
(4) To suppress secretions—atropine scopolamine
(5) Prophylactically to overcome undesirable anticipated side effects caused by the anesthetic agent.

Nervous System—Psychic sedation causes depression of cortex and calms patient. Analgesic drugs suppress pain and decrease reflex irritability. Second stage shortened when patients are sedated. Drugs depressing cortex, midbrain and other centers antagonize stimulating action of local anesthetics.

Respiratory System—Depressant drugs decrease O_2 consumption. Induction and maintenance of anesthesia with agents requiring high partial pressure are facilitated by this response.

Bronchi—Vagal reflexes from stimulation locally or manipulation of hilum inhibited.

Metabolism—Reduced by central nervous system depressant. Dosage of premedicating drug must be adjusted to following factors

(a) *Age*—Metabolic rate decreases with age. Less premedicating agent necessary. Metabolic rate highest in infancy

(b) *Sex*—Variation in metabolic rate between sexes of minor significance. Rate increased at puberty

(c) *Fever*—Increases metabolic rate markedly (7 calories per degree F.) Dosage may be increased.

(d) *Pain*—Increases metabolic rate. More premedicating agent required

Diseases of Metabolism—Thyrotoxicosis necessitates increased dosage of premedicating agent. hypothyroidism requires decreased dosage. Cachexia reduces metabolic rate profoundl

Mucous Secretions—Parasympathetic depressants (atropine scopolamine) inhibit salivary and mucous secretions.

Larynx—Spasms of central origin inhibited by parasympathetic depressant (atropine)

Circulatory System—Blood pressure and pulse approach normal due to release of psychic influence.

Prophylaxis—Parasympathetic drugs (atropine) given to counteract vagal stimulation. Drugs exerting pressor action given in anticipation of circulatory failure (ephedrine in spinal anesthesia)

Mesenteric Reflexes—Traction on visceral structures initiates circulatory and respiratory disturbances. Inhibited by atropine.

METHOD FOR VARIOUS TYPES OF ANESTHESIA

Inhalation Anesthesia—For adults of average size with normal metabolic rate use morphine gr ¼ atropine or scopolamine gr 1/100 intramuscularly one and one half hours prior to induction of anesthesia. May be administered intravenously 10 minutes prior to anesthesia. Dilaudid gr 1/30, demerol gr 1½ or methadon gr ¼ may be substituted. Decrease dose as age increases or if metabolic rate is reduced.

Regional Anesthesia—For adults of average size morphine gr ¼ and scopolamine gr 1/100 intramuscularly supplemented by a therapeutic dose of a short acting barbiturate such as pentobarbital or seconal. For spinal anesthesia the barbiturate is omitted.

For Intravenous Anesthesia—Morphine and scopolamine or atropine in the same manner as for inhalation anesthesia

For Psychically Disturbed or Extremely Apprehensive Patients—Basal narcosis with avertin, rectal or intravenous pentothal or evipal or paraldehyde may be used

For Subjects Intolerant to Morphine—Dilaudid, demerol, methadon or pantopon may be used

MORPHINE—ATROPINE

Morphine and atropine in the ratio of 25 parts to 1 respectively administered intravenously 10 minutes prior to anesthesia or subcutaneously one and one half hours prior to anesthesia produces the following effects

Cortex—Stimulant action of atropine antagonizes depressant effect of morphine. Alertness and mental keenness persist but somewhat obtunded. Amnesia not common unless large doses are used.

Respiratory Center—Stimulating effect of atropine antagonizes depressant action of morphine.

Vasomotor Center—Barely affected unless large doses are given.

Vagus Center—May be stimulated initially yielding bradycardia. Tachycardia may follow due to peripheral action of atropine on vagus.

Metabolic Rate—Reduced, but less than when morphine is used alone due to stimulant action of atropine.

Respiration—Moderate decrease in minute volume exchange. No effect on pulmonary tissue.

Skin—Dryness, flushing, absence of sweating frequently occurs.

Thalamus—Pain perception decreased due to analgesic action of morphine.

Eye—Miosis. Morphine effect usually predominates over dilating effect of atropine.

Secretions—Inhibited due to parasympathetic depressant action of atropine.

Heart—Some elevation in pulse rate frequently occurs. Tachycardia not common (vagal depression).

Blood Pressure—Usually reduced if elevated from excitement; no change otherwise.

Body Temperature—May be elevated due to effect of atropine centrally and on skin.

MORPHINE—SCOPOLAMINE

Morphine and scopolamine in the ratio of 25 parts to 1 respectively administered intravenously 10 minutes prior to anesthesia or subcutaneously one and one half hours prior to anesthesia produces the following effects

Cortex—Depression causing excellent sedative effect. Apprehension allayed. Amnesia frequent. Euphoria and feeling of well being common. Sedative effects of scopolamine are additive to those of morphine.

Vagus Center—May be stimulated initially. Usually no remarkable effect.

Vasomotor Center—Not affected ordinarily. Over-sedation may cause hypotension.

Respiratory Center—Depression caused by morphine is antagonized by scopolamine. Usually remains in preanesthetic state of excitation.

Respiration—Slight decrease in minute volume exchange. No notable effect on oxygenation.

Metabolic Rate—Decrease in oxygen consumption 10 to 15%.

Skin—Cool. No flushing or dryness.

Thalamus—Pain perception reduced due to analgesic action of morphine.

Eye—Morphine action predominates. Miosis common due to parasympathetic stimulation by morphine.

Secretions—Parasympathetic depressant action from scopolamine inhibits secretions and causes dryness of mouth.

Heart—No change in rate. Slowing occurs if tachycardia from excitement exists prior to anesthesia.

Blood Pressure—Reduced if elevation exists from excitement prior to anesthesia; otherwise no effect.

Body Temperature—No change. May be reduced.

SECTION XIV SOME CLINICAL CONSIDERATIONS

PRE-ANESTHETIC MEDICATION

Reasons for administering premedication and drugs used are as follows:

(1) For psychic sedation—barbiturates, opium alkaloids, avertin.
(2) To obtain an additive or synergistic effect—(opium alkaloids, demerol, procaine methadon) between drugs and contemplated anesthetic agents.
(3) To reduce reflex irritability and metabolic rate—opium alkaloids, avertin.
(4) To suppress secretions—atropine, scopolamine.
(5) Prophylactically to overcome undesirable anticipated side effects caused by the anesthetic agent.

Nervous System—Psychic sedation causes depression of cortex and calms patient. Analgesic drugs suppress pain and decrease reflex irritability. Second stage shortened when patients are sedated. Drugs depressing cortex, midbrain and other centers antagonize stimulating action of local anesthetics.

Respiratory System—Depressant drugs decrease O_2 consumption. Induction and maintenance of anesthesia with agents requiring high partial pressure are facilitated by this response.

Bronchi—Vagal reflexes from stimulation locally or manipulation of hilum inhibited.

Metabolism—Reduced by central nervous system depressant. Dosage of premedicating drug must be adjusted to following factors:

(a) *Age*—Metabolic rate decreases with age. Less premedicating agent necessary. Metabolic rate highest in infancy.

(b) *Sex*—Variation in metabolic rate between sexes of minor significance. Rate increased at puberty.

(c) *Fever*—Increases metabolic rate markedly (7 calories per degree F.). Dosage may be increased.

(d) *Pain*—Increases metabolic rate. More premedicating agent required.

Diseases of Metabolism—Thyrotoxicosis necessitates increased dosage of premedicating agent. hypothyroidism requires decreased dosage. Cachexia reduces metabolic rate profoundly.

Mucous Secretions—Parasympathetic depressants (atropine, scopolamine) inhibit salivary and mucous secretions.

Larynx—Spasms of central origin inhibited by parasympathetic depressant (atropine).

Circulatory System—Blood pressure and pulse approach normal due to release of psychic influence.

Prophylaxis—Parasympathetic drugs (atropine) given to counteract vagal stimulation. Drugs exerting pressor action given in anticipation of circulatory failure (ephedrine in spinal anesthesia).

Mesenteric Reflexes—Traction on visceral structures initiates circulatory and respiratory disturbances. Inhibited by atropine.

METHOD FOR VARIOUS TYPES OF ANESTHESIA

Inhalation Anesthesia—For adults of average size with normal metabolic rate use morphine gr ¼, atropine or scopolamine gr 1/100 intramuscularly one and one half hours prior to induction of anesthesia. May be administered intravenously 10 minutes prior to anesthesia. Dilaudid gr 1/30, demerol gr 1½ or methadon gr ⅙ may be substituted. Decrease dose as age increases or if metabolic rate is reduced.

Regional Anesthesia—For adults of average size morphine gr ⅙ and scopolamine gr 1/100 intramuscularly supplemented by a therapeutic dose of a short acting barbiturate such as pentobarbital or seconal. For spinal anesthesia the barbiturate is omitted.

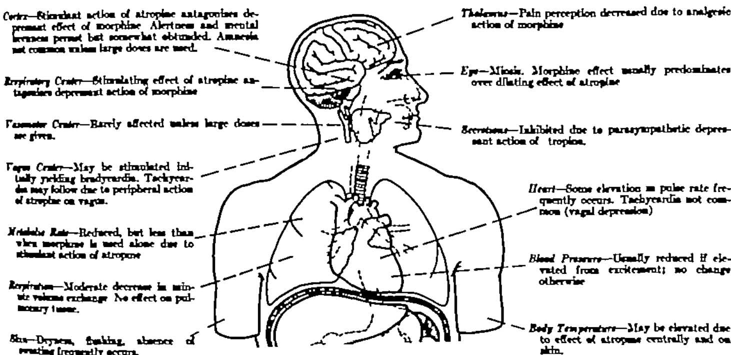
For Intravenous Anesthesia—Morphine and scopolamine or atropine *in the same manner as for inhalation anesthesia.*

For Psychically Disturbed or Extremely Apprehensive Patients—Basal narcosis with avertin, rectal or intravenous pentothal or evipal or paraldehyde may be used.

For Subjects Intolerant to Morphine—Dilaudid, demerol, methadon or pantopon may be used.

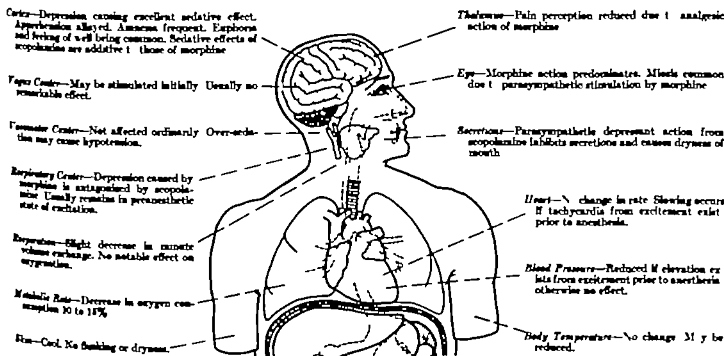
MORPHINE—ATROPINE

Morphine and atropine in the ratio of 25 parts to 1 respectively administered intravenously 10 minutes prior to anesthesia or subcutaneously one and one half hours prior to anesthesia produces the following effects



MORPHINE—SCOPOLAMINF

Morphine and scopolamine in the ratio of 25 parts to 1 respectively administered intravenously 10 minutes prior to anesthesia or subcutaneously one and one half hours prior to anesthesia produces the following effects



DEPTHS OF GENERAL INHALATION ANESTHESIA FOR SURGERY

Third stage of anesthesia required for surgery Divided into four planes or strata (after Guedel) as follows:

1st—Lid reflex or tone disappears, eyeballs oscillate pupils return to pre-anesthetic size inspiration equals expiration. (No remarkable circulatory changes)

2nd—Eyeballs fixed, pupils increase in size rhythmical respiration inspirations quickened, expiration prolonged. (No remarkable circulatory changes)

3rd—Eyeballs fixed progressive intercostal paralysis thoracic inspirations delayed expiration prolonged. (Circulation fails.)

4th—Pupils dilate diaphragmatic respirations; quick, jerky inspirations; prolonged expiration. (Circulation fails.)

Signs may vary with agent and subject pass in reverse on transition from deep to light anesthesia.

Craniotomy—1st plane no pain in handling brain. No relaxation required. Intratracheal tube necessary for airway

Mastoidectomy—1st plane sufficient; no relaxation required. Intratracheal tube desirable.

Myringotomy—1st plane should not be attempted without anesthesia.

Laryngectomy—Upper 2nd some muscle relaxation required.

Thoracic—1st and 2nd plane no muscle relaxation needed. Intratracheal catheter required.

Cholecystectomy—Lower 2nd plane, sometimes 3rd; adduction of vocal cords frequent, best relieved by intratracheal tube.

Nephrectomy—2nd and 3rd plane minor traction reflexes may be active Position often necessitates use of intratracheal tube

Ventral Herniorrhaphy—Lower 2nd plane, sometimes upper 3rd. Relaxation necessary

Appendectomy—2nd and 3rd plane.

Femoral and Inguinal Herniorrhaphy—2nd plane; some muscle relaxation needed.

Urological and Gynecological—Perineal, vaginal and cervical, 1st plane intra-abdominal, 2nd and 3rd planes.

Rectal—For sphincter relaxation, 3rd plane

Fractures—For bones attached to small muscles, 1st plane; to large muscles, 2nd plane.

Incision and Drainage—1st plane for superficial abscesses.

Ophthalmological—1st plane small muscles relax early in light second plane. 2nd plane if intratracheal tube is used.

Nasal and Plastic—1st plane sufficient, no relaxation required. 2nd plane if intratracheal tube is used.

Pharyngeal Airway—Tolerated in 1st plane intratracheal in 2nd plane.

Tonsillectomy—2nd plane relaxation of muscles necessary Intratracheal catheter desirable.

Thyroidectomy—1st plane no relaxation of muscles necessary Intratracheal catheter desirable.

Mediastinal Explorations—2nd plane. Intratracheal tube required.

Cardiac Surgery—2nd plane. Intratracheal tube required.

Diaphragmatic Surgery—3rd plane Intratracheal tube required.

Mastectomy—1st plane Muscle relaxation not necessary

Splenectomy—Lower 2nd or 3rd plane muscle relaxation required.

Gastric—Lower 2nd or 3rd plane muscle relaxation required.

Intestinal—During enteroanastomosis, upper 2nd or lower 1st plane, with deepening of anesthesia on closure; 2nd or 3rd plane for resections, little or no pain in handling viscera.

Obstetrical—Normal delivery analgesia or 1st plane forceps delivery 1st to 2nd plane; breech delivery 2nd plane version, 3rd plane Bandl's ring, 4th plane; Caesarean section, upper 2nd (abdominal muscles stretched, little relaxation needed).

Amputations—1st plane

Tenorrhaphy—1st plane for small muscles 2nd plane with large muscles. Nerves, 1st plane; large trunks, 2nd plane

Requirements for individual cases vary with subject, anatomical variations, and requirements of the surgeon

DEPTHS OF GENERAL INHALATION ANESTHESIA FOR SURGERY

Third stage of anesthesia required for surgery. Divided into four planes or strata (after Guedel) as follows

1st—Lid reflex or tone disappears, eyeballs oscillate; pupils return to pre-anesthetic size; inspiration equals expiration. (No remarkable circulatory changes.)

2nd—Eyeballs fixed; pupils increase in size; rhythmical respiration; inspirations quickened; expiration prolonged. (No remarkable circulatory changes.)

3rd—Eyeballs fixed; progressive intercostal paralysis; thoracic inspirations delayed; expiration prolonged. (Circulation fails.)

4th—Pupils dilate; diaphragmatic respirations; quick, jerky inspirations; prolonged expiration. (Circulation fails.)

Signs may vary with agent and subject; pass in reverse on transition from deep to light anesthesia.

Craniotomy—1st plane; no pain in handling brain. No relaxation required. Intratracheal tube necessary for airway.

Mastoidectomy—1st plane sufficient; no relaxation required. Intratracheal tube desirable.

Myringotomy—1st plane; should not be attempted without anesthesia.

Laminectomy—Upper 2nd; some muscle relaxation required.

Thoracic—1st and 2nd plane; no muscle relaxation needed. Intratracheal catheter required.

Cholecystectomy—Lower 2nd plane, sometimes 3rd; adduction of vocal cords frequent, best relieved by intratracheal tube.

Nephrectomy—2nd and 3rd plane; minor traction reflexes may be active. Position often necessitates use of intratracheal tube.

Ventral Herniorrhaphy—Lower 2nd plane, sometimes upper 3rd. Relaxation necessary.

Appendectomy—2nd and 3rd plane.

Femoral and Inguinal Herniorrhaphy—2nd plane; some muscle relaxation needed.

Urological and Gynecological—Perineal, vaginal and cervical, 1st plane; intra-abdominal, 2nd and 3rd planes.

Rectal—For sphincter relaxation, 3rd plane.

Fractures—For bones attached to small muscles, 1st plane; to large muscles, 2nd plane.

Incision and Drainage—1st plane for superficial abscesses.

Ophthalmological—1st plane; small muscles relax easily in light second plane. 2nd plane if intratracheal tube is used.

Nasal and Plastic—1st plane sufficient, no relaxation required. 2nd plane if intratracheal tube is used.

Pharyngeal Airway—Tolerated in 1st plane; intratracheal in 2nd plane.

Tonsillectomy—2nd plane; relaxation of muscles necessary. Intratracheal catheter desirable.

Thyroidectomy—1st plane; no relaxation of muscles necessary. Intratracheal catheter desirable.

Mediastinal Explorations—2nd plane. Intratracheal tube required.

Cardiac Surgery—2nd plane. Intratracheal tube required.

Diaphragmatic Surgery—3rd plane. Intratracheal tube required.

Mastectomy—1st plane. Muscle relaxation not necessary.

Splenectomy—Lower 2nd or 3rd plane; muscle relaxation required.

Gastric—Lower 2nd or 3rd plane; muscle relaxation required.

Intestinal—During enterostomies, upper 2nd or lower 1st plane with deepening of anesthesia on closure; 2nd or 3rd plane for re-sections, little or no pain in handling viscera.

Obstetrical—Normal delivery, analgesia or 1st plane; forceps delivery, 1st to 2nd plane; breech delivery, 2nd plane; version, 3rd plane; Bandl's ring, 4th plane; Caesarean section, upper 2nd (abdominal muscles stretched, little relaxation needed).

Amputations—1st plane.

Tenorrhaphy—1st plane for small muscles; 2nd plane with large muscles. Nerves, 1st plane; large trunks, 2nd plane.

Requirements for individual cases vary with subject, anatomical variations, and requirements of the surgeon

DISTURBANCES OF RESPIRATION

O_2-CO_2 Transport

Air—By volume composition is—

O_2	20 9%
N	78 0%
H_2O	1 0%
CO_2	0 04%
rare gases (not essential to life)	0 01%
dust, moisture	q.s.

Area of Alveoli—100 square meters.

Resting State of Lung—At end of expiration.

O_2 Tension—O_2 in alveoli, 13 5%—105 mm. Hg.

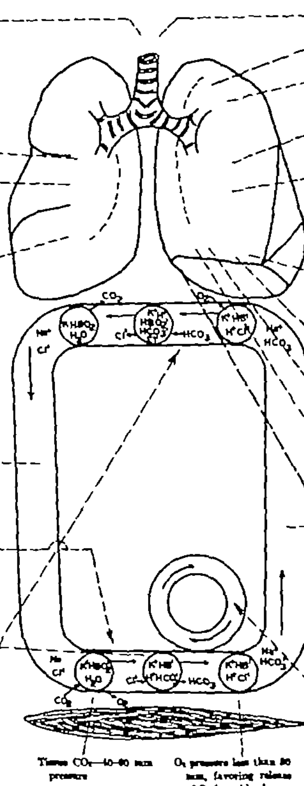
CO_2 Tension—CO_2 in alveoli, 5 1 to 5.5%, 40 mm. Hg average. Concentration varies 0 1 to 0 2% between inspiration and expiration; 60% tidal air mixes with alveolar air causing gradual variation of gas tensions along tract and preventing abrupt changes in concentration

Airway—Distance from lips to larynx—12 to 15 cms. length of larynx—4 to 5 cms. larynx to carina—12 to 14 cms.; diameter of trachea—2.5 cms. distances shorter in female than male and in children and young adults.

Blood CO_2—Total % arterial content CO_2—48 vols % venous—52 vols exists in three forms—dissolved—3 vols. % (0 1% as H_2CO_3, rest as free CO_2), carbamino—6 vols. %, and bicarbonate makes up remainder

Chloride Shift—CO_2 diffuses into cell, changed to H_2CO_3 in less than one second with aid of carbonic anhydrase; Cl ion from plasma diffuses in and bicarbonate diffuses out. K ion in cell from breakdown of oxyhemoglobin then becomes available to combine with Cl ion

Bicarbonate passes to lung with Na ion of plasma. O_2 forms oxyhemoglobin in cell which is more acid and which combines with K ion. Cl ion diffuses out bicarbonate ion diffuses in; same enzyme reverses action, liberating CO_2, which diffuses into plasma and alveoli.



Inspired Air O_2 Tension—158 mm. Hg.

Expired Air O_2 Tension—116 mm. Hg.

Resting Minute Volume Exchange—Eight to 10 liters per minute. May increase to 60 liters with exercise

Tidal Air—An ordinary inspiration or expiration at rest equals 500 cc.

Capacity of Lungs—Four to five liters total.

Dead Space—(Anatomical) Air space in trachea, pharynx and bronchi amounts to 150 cc. 33% of tidal air remains in dead space 66% mixes with functional residual air Physiological, virtual or effective dead space is total space in lungs which just prior to expiration contains perfectly fresh air

Vital Capacity—From onset of maximum inspiration to end of maximum expiration averages 3500 cc.

Reserve Air—From end of ordinary expiration to end of maximum expiration averages 1500 cc

Complemental Air—From end of maximum inspiration to end of quiet expiration averages 2000 cc

Residual Air—Air remaining in lung after maximum expiration averages 1000 cc.

Blood Volume—90 cc. per kilo.; plasma 50 cc. per kilo. O_2 carried by plasma —0.24 vols. % O_2 carried by hemoglobin—19 vols. %; 1 gm. hemoglobin carries 1.34 cc. O_2; normal hemoglobin equals 15 gms. per 100 cc., O_2 tension in blood—100 mm. Hg arterial blood, 95% saturated, venous blood saturation varies, averages 65%. A-V difference, 4 vols. %; pure O_2 quadruples plasma O_2.

Fetal Blood—Arterial blood carried by umbilical vein O_2 capacity averages 22 vols. %; 60% saturated; venous blood carried by umbilical arteries content 4 vols. % arterial blood total CO_2 content, 44 vols. %. CO_2 tension higher than maternal blood allowing outward diffusion O_2 tension lower than maternal, allowing inward diffusion.

ANOXIA

In acute anoxia three stages may be discerned (1) A *pre-crisis stage*—occurs when approximately 12 volumes per cent oxygen is present in arterial blood (2) a *circulatory crisis stage*—occurs when approximately 9 volumes per cent are present in arterial blood (3) a *terminal stage*—occurs when approximately 4 volumes per cent are present in arterial blood

Brain—Phylogenetically newer cells most sensitive of all tissues due to high rate of oxygen consumption. Progressive depression of central nervous system from above downward occurs as degree of anoxia increases. Phylogenetically older portions of brain more resistant than newer

Midbrain—Depressed. More resistant than the cortex.

Medulla—Reflexly stimulated by mild anoxia (pre-crisis stage). Depressed in terminal stage. Centers depressed. Respiratory center before vasomotor. Vagus center least.

Respiratory Movements—Pre-crisis stage: Increase in both depth and rate (also aortic stimulation). Crisis stage: regular breathing ceases asphyxial gasps appear. Terminal stage: respiration ceases.

Metabolism—Affected. Usually depressed

Liver—Impairment of function occurs, depending upon duration and severity of anoxia and state of organ.

Adrenal—Epinephrine content of gland depleted by mild anoxia. Signs of sympathetic stimulation appear

Cortex—Highly sensitive to oxygen deprivation. Motor cells irritated causing various neuromuscular phenomena.

Eye—Nystagmus at first. Eyeball fixed. Pupils dilate due to depression of centers. Corneal reflexes and light reflexes lost in crisis stage

Trachea—Spasm of vocal cords in crisis stage. Relaxed in terminal stage

Salivary Glands—Yield scant amount of thick mucus.

Blood Pressure—Pre-crisis stage: Systolic increases, diastolic unaltered or lowered. Pulse pressure increased. Crisis stage: Systolic falls. Terminal—rapid fall to zero of both systolic and diastolic

Heart—Pre-crisis stage: Acceleration due to diminution of vagal tone. Heart dilates. Crisis stage: Bradycardia suddenly occurs, mediated by cardio-inhibitory nerves. Gradually as anoxia increases pulse rate increases (cardio-inhibitory center is depressed). Terminal stage: Direct depression of myocardium occurs. Slowing followed by asystole

Venous Pressure—Rise in venous pressure in pre-crisis and in crisis stage

Spleen—Constricted due to sympathetic stimulation. Red cells pass into systemic circulation.

Stomach—Hunger contractions decreased. Secretions not inhibited.

Intestines—Motility depressed.

Muscles—Twitchings followed by contractions, opisthotonos, torsion spasm, extensor spasm and generalized convulsions are manifestations of cortical irritation. Central nervous system depressants may soften or completely mask them.

Skin—Cyanosis appears when concentration of reduced hemoglobin exceeds 5 grams %. Intensity varies with
(1) calibre of cutaneous vessels,
(2) thickness of skin,
(3) amount of pigment in skin,
(4) acuity and color perceptions of observer
Skin temperature reduced. Vessels constricted.

BLOOD

Total Volume—Reduced. Capillary permeability increased.

Red Blood Cells—Increased. Result of hemoconcentration.

Carbon *Dioxide Content*—Reduced at first due to hyperventilation. May increase later

Carbon *Dioxide Combining Power*—Reduced due to liberation of fixed acids.

Lactic Acid—Increased, due to oxygen debt.

Glucose—Increased due to glycogenolysis.

Clotting—Blood remains in fluid state post mortem

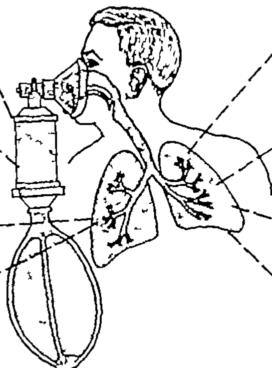
Symptoms and effects of anoxia vary from individual to individual and with degree and duration. Anesthesia modifies signs and symptoms of anoxia. Anoxia is O_2 lack without impedance to CO_2 elimination. Asphyxia denotes impedance to CO_2 and O_2 exchange

TYPES OF ANOXIA

1. *Anoxic*—Amount of oxygen passing through the alveolar membrane insufficient to saturate completely blood in pulmonary vascular bed. Content and tension reduced
2. *Stagnant*—Amount of oxygen delivered to tissues insufficient due to poor circulation. Content and tension normal.
3. *Anemic*—Amount of oxygen carrying pigment reduced Content decreased tension normal.
4. *Histotoxic*—Ability of cells to utilize oxygen reduced Blood oxygen content normal or increased

CAUSES OF ANOXIA OR ASPHYXIA

1. Insufficient oxygen in inhaled mixture
2. Reduced tidal exchange (anoxic anoxia) May be caused by depressed respiratory center or carotid body intercostal paralysis, convulsions, compression of thorax, pneumothorax, hydrothorax, pyothorax, Trendelenburg and other positions which inhibit respiratory motion.
3. Obstruction. Secretions, relaxed tongue or muscles, spasm of vocal cords from various causes such as excessively high concentration of the drug, blood, vomitus, canister dust, CO_2, foreign body tracheal collapse or neoplasms encroaching upon trachea or bronchi and bronchospasm from allergic states or effect of the drug.
4. Decreased vital capacity (anoxic anoxia) Pulmonary decompensation due to emphysema, neoplasm, fibrosis or suppurative disease.



5. Interference with diffusion (anoxic anoxia) Edema of alveolar membrane, excessive secretions, emphysema or inflammatory lesions.
6. Failure of transport system (stagnant anoxia) Myocardial insufficiency prolonged circulation time due to shock or hemorrhage, obstruction to blood flow due to emboli from air fat or clots.
7. Decrease in oxygen carrying power (anemic anoxia) Anemia, reduced blood volume, alteration in hemoglobin such as carbon monoxide hemoglobin.
8. Disturbances of tissue respiration (histotoxic anoxia)—cyanides and anesthetics may inhibit respiratory enzymes.

SYMPTOMS OF CEREBRAL DAMAGE

Ordinarily occur after a bout of acute anoxia which was characterized by both respiratory and circulatory failure Dilatation of the cerebral vessels and stasis occurs.

Immediate Signs—Slow bounding pulse, irregular gasping respiration, followed by apnea. After resuscitation, coma, followed by twitching of small muscles, convulsions and muscle rigidity occur. Hyperthermia within six to 48 hours is usual terminal event (108° to 110°F not uncommon).

Delayed Signs—Gradual emergence from above picture Stupor mental cloudiness, with gradual recovery Parkinsonism, blindness, or psychoses often occur May be transient, lasting weeks or months, or permanent.

Pathological Effects of Asphyxia—Cerebral damage follows respiratory and circulatory failure or protracted bouts of asphyxia. Petechial hemorrhages may be found on serous surfaces of various organs due to changes in capillary permeability in acute asphyxia. No changes elsewhere

When death is delayed changes are found in brain. Occur mostly in cortex, cerebellum and basal ganglia, but may appear anywhere in the C.N.S.

PATHOLOGICAL CHANGES IN BRAIN

CORTEX

Earliest Changes—Occur several hours after respiratory and circulatory failure. Widened perivascular and pericellular spaces most common finding.



Late Changes—Death of cells followed by vacuolization and confluence of areas of necrosis.

Healed—Necrotic areas replaced by scar tissue Nervous elements do not regenerate. Similar changes noted if death is delayed for weeks or months.

Nerve Cells—Pyramidal and Purkinje's cells undergo acute degeneration. Chief findings are swelling of cytoplasm, nuclear degeneration and disappearance of Nissl substance followed by necrosis.

Interstitial Cells—Changes occur in microglia. Astrocytes proliferate and oligodendroglia swells.

Meninges—Adhesions between pia, arachnoid, and dura follow inflammatory changes resulting from death of tissues.

EFFECTS OF ANOXIA ON CIRCULATION AND RESPIRATION DURING INHALATION ANESTHESIA AND HYPNOSIS WITH NON VOLATILE DRUGS

Agent	Crisis Stage					Terminal Stage			
	Blood Pressure	Heart Rat	Vagal Tone	Respiration Asphyxial gasping	Chemoreceptor Activity	Blood Pressure	Heart Rate	Vagal Tone	Respiration
Nitrogen	Elevated	Slowed	Increased	Present	Active	Falls	Slowed	Decreased	Ceases
Nitrous oxide	Elevated	Slowed (vagal effect)	Increased	Present	Active	Falls	Slowed, followed by asystole	Depressed	Ceases
Nitrous oxide Atropine Morphine	*Elevated*	*Increased*	*Depressed by the premedication*	*Asphyxial gasping does not appear*	*Depressed*	*Falls*	*Slowed, followed by asystole*	*Depressed*	*Ceases*
Nitrous oxide Scopolamine Morphine	Elevated	Increased	Depressed by premedication	Present mildly masked	Mildly depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Nitrous oxide Pentobarbital	Elevated	Increased	Depressed by barbiturat	Absent	Depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Nitrous oxide Amytal	Elevated	Increased	Depressed by barbiturat	Absent	Depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Ether III 1 & 2	Elevated	Slowed (vagal)	Increased	Present	Mildly depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Ether III 3 & 4	Elevated	Increased	Depressed by drug	Absent	Depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Pentothal	Elevated	Increased	Depressed by drug	Absent	Depressed	Falls	Slowed, followed by asystole	Depressed	Ceases
Cyclopropane	Elevated	Slowed (vagal)	Increased	Present	Active	Falls	Slowed, followed by asystole	Depressed	Ceases
Chloroform	Elevated	Slowed (vagal)	Increased	Present	Active	Falls	Slowed, followed by asystole	Depressed	Ceases
Demerol	Elevated	Slowed	Increased	Present	Active	Falls	Slowed, followed by asystole	Depressed	Ceases

"Slow bounding pulse" and asphyxial gasping are obtunded by certain agents and premedication, thereby increasing possibility of passing without warning from pre-crisis to crisis stage

ALTERATIONS IN PULMONARY PHYSIOLOGY DURING GENERAL ANESTHESIA

Anatomic Dead Space—Increased by agents which decrease bronchiolar tone, decreased by agents which increase bronchiolar tone.

Physiologic Dead Space—Increased by increased tidal volume or mechanical ventilation.

Diffusion Respiration—Interchange of gases between blood, alveoli and upper respiratory tract which occur in the absence of respiratory movements. Induced by having high O_2 partial pressure in upper respiratory tract. Alveolar O_2 combines with hemoglobin decreases alveolar pressure and causes inward diffusion of O_2 (called hemoglobin pump). Outward diffusion of CO_2 occurs but more slowly. Results in CO_2 retention and severe metabolic acidosis.

Diffusion Anoxia—Anoxia resulting from outward diffusion into the alveoli of highly soluble gases administered at high partial pressures. Occurs when N_2O anesthesia is interrupted and air breathing is commenced. One volume of poorly soluble N_2 replaces 30 volumes of N_2O from blood. Lung gains gas volume. Outward rushing of excess gas dilutes O_2 in lung. Causes anoxia.

Remedy: Terminate anesthesia inhaling 100% O_2.

Minute Volume—Decreased due to central depression and decreased metabolic needs.

Resistance—Impedance to passage of respiratory gases. Varies with bronchiolar diameter viscosity density and degree of turbulence of gases, and mechanical factors in inhaler. Increased resistance necessitates increase in respiratory effort.

Inspiratory Resistance—Necessitates increased respiratory effort to maintain normal minute volume exchange and blood gas tensions. Causes increase in negative pressure in alveoli and pleural space. May lead to pulmonary edema.

Expiratory Resistance—Less fatiguing than inspiratory. Agents which increase bronchiolar tone decrease anatomic dead space.

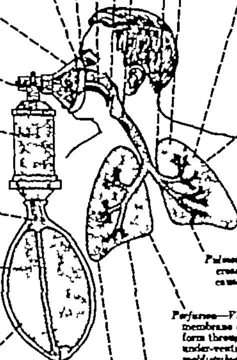
Controlled Respiration—Artificially maintaining pulmonary ventilation by deliberately inducing apnea. Apnea produced by (1) combination of (a) reducing CO_2 tension (hyperventilation) (b) depression of respiratory center with drugs (cyclopropane and a narcotic) (c) stimulation of stretch reflexes, or (2) neuromuscular blockade (curare). May increase physiologic dead space during manipulation.

Positive Pressure—Sustained positive pressure causes decreased venous return and decreased cardiac output. Intermittent positive pressure less deleterious if deflation time exceeds inflation time and inflation pressure returns to normal.

Negative Pressure—May result in collapse of respiratory bronchioles in pathological states emphysema.

Effect of Body Position—Supine prone or lateral causes decrease in functional residual air volume.

Lateral—upper lung under-perfused and over-ventilated. Dependent portions under-ventilated, over-perfused. Dead space increased, CO_2 retained.



Upper Respiratory Tract Reflexes—Mediated via the vagus nerves. Stimulation by pungent agents (ether, chloroform) reflexly inhibits inspiration. May cause apnea and glottic spasm. Less pronounced stimulation by gases.

Lower Pulmonary Tract Reflexes—Receptors (stretch) activated by distention and by collapse (deflation). Served by vagus. Vapors (ether chloroform, fluothane, trichlorethylene, etc.) sensitize both stretch and deflation receptors. Augment ventilation. Sensitization by gases insufficient to augment ventilation.

Extra-Pulmonary Sensory Receptors—Sensory receptors (in muscle, joints, etc.) communicating with respiratory system stimulated by blood borne anesthetics and augment respiration (ether).

Lung Volume—Varies. Probably decreased during general anesthesia. Functional residual air capacity less in supine than erect or lateral position. Stretch receptors reflexly alter resting lung volume during positional changes.

Compliance—Stretch-ability of lung. Defined as volume change of lung and thorax per unit of pressure change at zero air flow. Expressed in liters per cm. H_2O pressure between trachea and pleura. Compliance varies with (1) elasticity of lung, (2) lung blood volume, (3) tone of thoracic muscles cage, (4) total lung tissue mass, (5) tendency of alveoli to collapse, (6) bronchial tone. Increase in compliance necessitates increase in respiratory effort.

Alterations during anesthesia variable. Generally decreased. Factors favoring decrease are: (1) Bronchial obstruction (constriction, secretions, mucosal edema) (2) vascular stasis due to effects of agents, (3) changes in skeletal muscle tone, (4) influences of vagal reflexes (stretch-deflation) (5) mechanical factors causing uneven ventilation of lung.

Pulmonary Circulation—Pulmonary vascular resistance increases during anesthesia (ether). Lung inflation also causes increase.

Perfusion—Ventilation Ratios—Gas transfer across pulmonary membrane optimal when ratio of blood flow to gas flow is uniform through all areas of lung. Under-perfusion, over-perfusion, under-ventilation or over-ventilation in any area results in maldistribution. Maldistribution alters O_2 and anesthetic gas uptake and CO_2 elimination. Over-perfused (under-ventilated) areas result in less anesthetic and O_2 uptake. Equivalent to creation of A.V. shunt. Under-perfused (over-ventilation) equivalent to increase in alveolar dead space. Hypoventilation causes increased alveolar CO_2 and change in gradient from blood to alveolar air due to collapse of some alveoli.

Open Pneumothorax—Results in maldistribution. Over-perfused and under ventilated in collapsed lung. Blood gas tensions disturbed. Respiratory acidosis, anoxia due to creation of shunts and collapsing of alveoli.

Closed Pneumothorax—May cause greater distress by collapse of lung due to tension.

RESPIRATORY ACIDOSIS DURING GENERAL ANESTHESIA

DEFINITION—Elevation in CO_2 tension total acids of blood and decrease in blood pH due to faulty elimination of CO_2.

Causation During Anesthesia—Hypoventilation from depressed respiratory center impaired ventilation due to maldistribution of gases, improper pulmonary perfusion, obstruction and other mechanical factors. Occurs with all anesthetics. Least with ether

Central Nervous System—Carbon dioxide excess depresses all areas. An additive effect results with anesthesia. Arterial blood ether concentration for given E.E.G. level less due to additive effects of CO_2. May produce convulsions if pyrexia and metabolic acidosis complicate anesthesia.

Vagus—Respiratory acidosis enhances the effect of vagal stimulation on the heart.

Carotid Body—Remains active Stimulated only by very high CO_2 tensions.

Ventilatory Effects—Variable. Hypoventilation usually present. Hyperpnea uncommon due to depression by agent Hypoventilation enhanced by non-volatile hypnotics and narcotics. Respiration may be gasping in severe states

Alveolar CO_2 Tension—Elevated. May rise from 47 to 190 mm. Hg in severe states. Average increase 15–60 mm. Hg above normal.

Diaphragm—Spasmodic jerking of diaphragm (hiccough)

Metabolism—Some suppression of liver functions Ability of liver to metabolize thiopental decreased by hypercardia.

CO_2 Output—Total output decreased due to increased metabolism Concentration of expired gas increases. V ries with degree of ventilation (4 8%—3-4 normal)

Kidney—Increased excretion of acid. Loss of base results Prolonged respiratory acidosis may merge int metabolic acidosis Ketone bodies not increased

Skin Temperature—Elevated due t peripheral vasodilatation Cyanosis basent in face of adequate O_2 intake

Intracranial Pressure—Increased. Cerebral vessels dilated Cerebral blood flow increased.

Pupils—No change in size. Activity of ocular reflexes diminished due to effects of carbon dioxide narcosis on anesthesia.

Heart—In mild degrees of acidosis no change In severe cases marked bradycardia nd irregularities in rhythm occur Increases in amplitude of T waves. Abrupt decrease in CO_2 may cause cardiac standstill or ventricular fibrillation. Gradual decrease may not. Contractile force of the heart decreased in severe acidotic states.

Blood Pressure—Peripheral resistance increases as CO_2 tension becomes elevated. Pressure elevated. Abrupt lowering of CO_2 tension causes sudden reduction in blood pressure below base-line—hypotension results. Diastolic decreased abruptly Decrease varies with degree of CO_2 accumulation. Hypotension results from sudden withdra al of *vasoconstrictor reflex and persistence* of local vasodilator effect of hypercarbia. May follow anesthesia with any agent during which CO_2 retention occurs.

Central Venous Pressure—Increased. Reduction if hypotensive state develops.

Arterioles—Dilated. Effect persists after withdrawal of excess CO_2. Contributes t hypotension after removal of central vasoconstrictor drive.

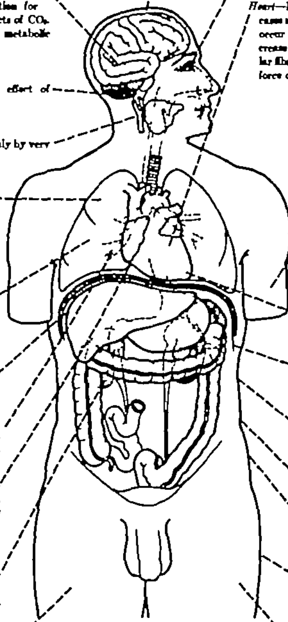
Capillaries—Dilated by CO_2 excess. Contributes to increased oozing.

Clotting Time—Shortened.

Electrolytes—Arterial blood pH decreased below 7 Plasma potassium rises May reach 7 0 or more M.Eq Base lost into urine

Effect of Posture—Lateral and other restrictive positions favor retention of CO_2 by causing maldistribution of perfused blood and alveolar gases.

Body Temperature—Decreased body temperature favors CO_2 retention due to increased solubility plasma (hypothermia)



THE ELECTROENCEPHALOGRAM IN ANESTHESIA

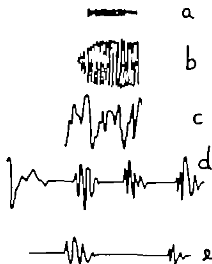
DEFINITION—The brain produces electrical activity measurable in terms of potential. Electroencephalogram is a graphic record of the sum of the voltages developed by individual neurons in a particular area of the cerebral cortex. Usually the activity of an area of the cortex is measured. Origin of electrical activity of cortex not fully understood. Presumably rhythms represent fluctuating potentials produced by dendrites. Minute electrical impulses passing *through* intact skull and scalp are gathered by electrodes and conducted through amplifiers. Amplified current operates a system of levers which records variations in intensity of current graphically with ink-writers. Current rises from zero to maximum, reverts back to zero many times per sec., resulting in a tracing consisting of waves called cycles. Height (amplitude) of wave is governed by voltage developed. Number of waves (frequency cycles) varies with different stages of activity. Normally three wave patterns are noted. (1) Alpha (awake with eyes closed) about 10 cycles per sec., 50 millivolts—obtained from occipital areas. (2) Beta—20 to 50 cycles per sec. 5–10 millivolts. (3) Delta—1 to 5 cycles per sec., voltage increased 20 to 200 microvolts—occurs in sleep and in pathologic states in awake persons.

HISTORY—Electrical activity first noticed by Caton (1875). Von Marxow first studied alterations caused by chloroform (1890). Hans Berger (Jena, 1929) founded science of electroencephalography. Gibbs and Lennox (1937) suggested electroencephalogram might be applicable to anesthesia. Rubin and Freeman (1940) studied changes during cyclopropane anesthesia. Brazier and Finesinger (1945) studied effects of barbiturates on cortical potentials. Beecher and McDonough studied cortical potentials with seventeen anesthetic agents (1939). Bickford and Faulconer (1950) classified electroencephalographic changes produced by ether and other anesthetics.

USES IN ANESTHESIA

Cortical potentials altered by central nervous system depressants. Suppressed as depression increases. Suppression is proportional to the quantity in the brain. Changes produced are (1) reproductible for given drug in given patient, (2) vary little from person to person for given drug, (3) the discharge is serial—disappears and reappears in same manner as concentration is varied, (4) response is rapid.

Clinical signs of reflex activity (Guedel) lag behind return of cortical activity in reversal. (5) The brain discharges as a unit. Local differences disappear and synchronization of activity of the cortex appears. (6) Rhythm amplified. (7) The stages of depression are correlated with blood concentration (volatile drugs).



BASIC CHANGES IN PATTERN

Basic changes in pattern are common to many drugs. These are

(a) Increase in frequency in 20–30 cycles per sec. No voltage change (as consciousness is lost).
(b) Small waves rapid, replaced by larger (5–300 microvolts) at slower rhythm 1–5 cycles per sec. as consciousness is lost.
(c) Fast low voltage waves superimposed on background of high voltage, low frequency. Also known as *mixed pattern*.
(d) Voltage decreases, frequency decreases with periods of inactivity interposed between periods of activity. Inactivity separated by activity called *burst suppression*. Interval of inactivity becomes longer and number of waves decreases as anesthesia deepens.
(e) Loss of activity, flat tracing or low voltage very slow rhythm occurs in overdosage.

TECHNICAL DIFFICULTIES

Satisfactory results not obtained because the current is amplified million or more times and the following produce strong potential and cause artefacts.

(1) Movement of the electrodes
(2) Improper placement of the electrodes
(3) Mechanical defect of apparatus
(4) 60 cycle interference
(5) Muscular movements
(6) Movement of the patient
(7) Movement of the cables
(8) Cardiac current artefacts
(9) Cardiac current amplified

USES OF ELECTROENCEPHALOGRAM IN ANESTHESIA

1. During whole body perfusion to detect cerebral perfusion.
2. To assess cerebral damage after anesthetic accidents (cardiac arrest).
3. Detect changes in cortical activity during hypothermia.
4. To detect changes in depth of anesthesia when all other methods are ineffective.
5. For the use in clinical and laboratory study of new agents.

VARIATIONS WITH INDIVIDUAL AGENTS

I. VOLATILE ANESTHETICS

A. Gases

Nitrous Oxide—70% N_2O–30% O_2 produces, under pressure wave forms of 5–70 cycles per sec and increased amplitude. Waking frequencies replaced by slow waves 2–4 cycles per sec and increase in amplitude up to 40 to 70 microvolts. Burst suppression not seen.

Ethylene—Suppression similar to nitrous oxide.

Cyclopropane—Six levels of activity. First five similar to ether. Amplitude less. Level VI absent waves—flat line results.

Xenon—Levels not differentiated. Total suppression not seen. Slowing of the rhythm and increased voltage. Burst suppression not seen.

B. Liquids

Ether—Seven levels.

Level I—Alpha waves converted to low amplitude wave form of 50 microvolts and increased frequency 20–30 cycles per sec. (lasts 7 minutes).

Level II—Abrupt appearance of slow waves 2–8 cycles per sec. High amplitude 200–800 microvolts (lasts 60 sec.)

Level III—Rhythmicity lost. Mixed pattern appears. Slow waves with faster waves of decreased amplitude superimposed. No suppression.

Level IV—Burst suppression appears. Maximum duration 3 sec. Waves 2–4 cycles per sec. Average amplitude 150 microvolts.

Level V—Increase in suppression time 3–10 sec. Intervening waves single, smaller amplitude.

Level VI—Activity reduced to less than 1 in 10 sec. Irregular amplitude about 70 microvolts.

Level VII—Complete suppression. Activity less than 20 microvolts. Waves absent.

Divinyl Ether (Vinethene)—Classification of levels not available in humans.

Fluoroxenyl Ether—Six patterns.

Pattern I—Alpha rhythm replaced by activity 15–25 cycles per sec. Voltage decreased below 25 microvolts.

Pattern II—Frequency 4–6 cycles. Low voltage up to 80 microvolts. Spindles of 6–8 sec superimposed on fast activity of previous level.

Pattern III—Fast background activity ceases. Dominant waves increase in voltage and frequency. Regular waves 3–8 cycles. Amplitude 75–125 microvolts.

Pattern IV—Irregular large slow waves 100–200 microvolts, 2–4 cycles per sec.

Pattern V—Dominant forms fairly regular. High voltage, long duration, every 1–2 sec. Spread of 1 sec. Voltage from 100–150 microvolts. Superimposed on faster waves of 3–5 cycles per sec. in amplitude of 25–75 microvolts.

Pattern VI—Dominant slow wave frequency disappears to 1 every 2 sec. Superimposed waves of 3–5 cycles per sec. Decreased from 25 to 15 microvolts.

Chloroform—Six levels.

Level I—Slow frequency, higher amplitude wave pattern superimposed against fast-low amplitude background activity.

Level II—Low voltage, rapid activity.

Level III—Low voltage activity 20–30 cycles per sec.

Level IV—Delta type waves. Slow rhythm with high voltage.

Level V—20–30 cycles rhythm ends, slow wave dominant appears.

Level VI—Decrease in amplitude of slow waves and decrease in frequency.

Trichlorethylene with nitrous oxide—Three levels.

Level I—Amplitude diminished from the wake tracing. Frequency increased as analgesia and unconsciousness ensue.

Level II—Rhythmic. Large, slow waves in amplitude of 100–200 microvolts, frequency 3 to 5 cycles per sec.

Level III—Frequency low, amplitude high. Rhythmicity disappears.

Ethyl chloride—Decreased frequency and increased amplitude.

Fluothane—Seven levels.

Level I—The waking wave pattern changes to fast, low voltage 15–30 cycles, 10–25 microvolts.

Level II—Slow waves 3–6 cycles, amplitude 80 microvolts. Fast, low voltage activity superimposed.

Level III—Slow waves 4 cycles per sec. Amplitude 5–100 microvolts. Fast activity disappears.

Level IV—Fast activity disappears. Slow waves of amplitude 100–300 microvolts, frequency 2–3 cycles per sec. Notched and irregular.

Level V—Slow waves 1 cycle per sec, amplitude of 100–300 microvolts. Intervening smaller and faster waves in amplitude of 25–50 microvolts, frequency 6–8 cycles per sec.

Level VI—Slow wave frequency 1 cycle per 2–3 sec. Interposed and superimposed waves of 6–8 cycles, amplitude of 25 microvolts. Burst suppression appears.

Level VII—Complete suppression and absence of wave forms.

1

II. NON VOLATILE DRUGS

A. Hypnotics

Amylene Hydrate—Decreased activity. Levels not described.

Barbiturates—Sedative doses no change.

Phenobarbital—Large waves 14 cycles per sec. with sleep. Burst suppression with narcosis.

Thiopental—Five levels.

Level I—High amplitude 75–80 microvolts, fast frequency 10–20 cycles per sec., spiky.

Level II—Complex. Slow waves, irregular contour, random occurrence of frequency from 2 cycles upward, amplitude up to 150 microvolts. "Spiky" waves with irregular amplitude and frequencies of 10 cycles superimposed on slow waves.

Level III—Suppression less than 3 sec. duration. Biphasic bursts. First phase 1 sec. frequency 10 cycles. Second phase 2 cycles merging into next suppression.

Level IV—Marked suppression 3–10 sec. Activity similar to III but less amplitude.

Level V—Activity every 10 sec., amplitude less than 25 microvolts.

Hydroxydione (Viadril)—Four levels.

Level I—Suppresses alpha activity. Slow waves 4–6 cycles per sec. Increased amplitude.

Level II—Compound pattern 3–12 cycles per sec. Amplitude 6–100 microvolts. Superimposed low fast activity with spiky effect.

Level III—Burst suppression several sec. duration.

Level IV—Widely spaced burst of activity of less than 20 microvolts, appearing in flat tracing.

B. Narcotics

Morphine—No significant effect. Analgesic doses.

Methadon—Analgesic doses no effect.

Meperidine—No effect.

Chlorpromazine—(25 mgm.) Fast activity induced by intravenous injection. Oral no effect. Decreased amount of ether necessary for Level IV.

C. Analeptics

Bemegride—Reverts pattern produced by barbiturates to wider patterns of light narcosis. Alone similar effects as a convulsant.

Levallorphan—Further slowing of frequencies when used with N_2O and meperidine. No reversal of cortical pattern.

Caffeine—No effects.

D. Muscle Relaxants

Curare—No effects.

Erythroidine—No effects.

Gallamine (Flaxedil)—No effects.

Decamethonium—No effects.

Succinyl Choline—No effects.

E. Miscellaneous Drugs

Ergotamine—No effects.

Histamine—No effects.

Vasopressin (Pitressin)—No effects.

Sodium Nitrite—No effects.

Phenylephrine (Neosynephrine)—No effects.

Epinephrine—No effects.

F. Premedication

Atropine—1/100–1/150 grain I.V. causes decrease in voltage of all waves, followed by bursts of high voltage waves with 10 cycles per sec. Bursts appear at 10 sec. intervals, last 1–3 sec.

G. *Anoxia*—Electroencephalograph useful for detecting anoxia particularly for extracorporeal perfusion. Changes significant. Tracings of prognostic value.

Anoxic Anoxia—Increase in rate and of amplitude of waves followed by pronounced slowing. Great increase in amplitude. Finally decline to a flat tracing.

Stagnant Anoxia—Same as anoxic. Inhalation of 6–11% oxygen. Small, fast activity within 60 seconds replaced by slow large waves. Recovery in reverse order.

H. *Hypotension*—Inadequate cerebral perfusion results in changes characteristic of anoxia. Depression of high voltage fast activity as pressure declines. Cortical activity ceases at levels 20 mm Hg. Vasopressors restore rhythm toward normal.

I. *Hypothermia*—Usually negligible change. Tendency towards slowing of frequency not greater than 25%. Occlusion of circulation results in superimposed low voltage, fast frequency activity developed and persisted after cessation of lower frequencies. Becomes isoelectric for duration of occlusion. After release activity reappears and gradually returns to pre-occlusion level. Low voltage, fast frequency activity (file pattern) occurs during recovery from occlusion.

J. *Hypoglycemia*—Decrease in alpha activity reversible with ingestion of sugar. Insulin coma causes abrupt appearance of large, slow waves as consciousness is lost. Severe hypoglycemia abolishes cortical activity.

K. *Hyperglycemia*—No change.

DELIBERATELY INDUCED HYPOTENSION DURING ANESTHESIA AND OPERATION

SYNONYMS—Controlled hypotension Hypotensive anesthesia purposefully induced hypotension

DEFINITION—Deliberate induction of a disparity between the circulating blood volume and the size of the vascular bed. Accomplished by (1) decreasing the blood volume or (2) relaxing vascular bed by decreasing peripheral resistance by denervation of vascular innervation by blockade or chemical agents.

RATIONAL—Tolerance to hypotension due to blood loss appears to be greater in subjects with decreased peripheral resistance Onset of irreversible shock delayed. Normal capillary pressure remains unchanged—32 mm. Hg Reduction in peripheral resistance favors maintenance of normal capillary pressure and permits blood to flow even though systolic blood pressure is reduced Perfusion remains adequate.

HISTORY—Morton (England) 1900 used total spinal block for operation Also Koster (1926) Jonnesco, Kolkstadht and Page used it experimentally to study shock in surgical procedures. First used by Gardner and Hale (Crile Clinic) 1946 by technique of arteriotomy Total spinal techniques first used by Gillis (England) 1948 Davison and Elderly (England) 1950 used hexamethonium and Nicholson, Sarnoff and Crehan (Boston) used thiophanium (Arfonad) for ganglionic blockade Bromage Hingson advocated use of peridural block. Phemister first demonstrated benefit of vascular denervation in rabbits.

INDICATIONS SURGICAL

(1) To obtain "dry field."
(2) Conserve blood (rare types)
(3) Reduce organ tension (brain, liver kidney)
(4) Avoid transfusions.
(5) Reduction of intravascular tension.
(6) Control of hypertensive crises.
(7) Obtundation of autonomic stimuli.

INDICATIONS MEDICAL

(1) Combat pulmonary edema.
(2) Decrease cerebrovascular bleeding
(3) Decrease venous congestion in cardiac failure.
(4) To decrease sympathetic over-activity
(5) To combat pain due to vasospasm.

SITES OF VASCULAR DENERVATION AND METHODS OF REDUCING BLOOD VOLUME AND PERIPHERAL RESISTANCE

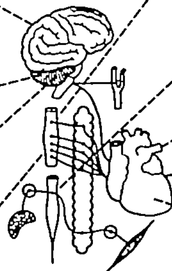
Autonomic Centers—Depression of vasodilator impulses from autonomic centers in midbrain and thalamus. Hydralazine (Apresoline) believed to act at this site Not practical for use during operation.

Autonomic Ganglia—Chemical blockade by systemic use of hexamethonium, pendiomide, thiophanium (Arfonad) Feasible and technique of choice for operation.

Medullary Centers

(a) *Vasomotor Center*—Depressed by excess of narcotics (morphine) basal hypnotics (barbiturates) or anesthetics. Not practical—respiratory and other vital centers depressed simultaneously

(b) *Vasodilator Center*—Stimulated-increasing number of dilator impulses Veratrum alkaloid act in this manner Not practical for use during anesthesia.



Adrenergic Receptors—Blockade of sympathetic effector cells by sympatholytic and adrenolytic drugs—ergotamine priscoline, phenothiazine derivatives. Blockade difficult to reverse with stimulants because of persistent blockade. Not controllable

Arteriolar Smooth Muscle—Depression by nitrites, local anesthetics and other smooth muscle depressants. Not practical. Not readily controllable with available agents.

Capillaries—Increase in permeability causes fluid to be lost from vascular space into extracellular space (Histamine)—Not controllable reversible or practical.

Heart—Depress myocardium and reduce cardiac output (15–40%). Vasoconstriction present. Perfusion inadequate in peripheral vessels.

...nic *Preganglionic Fibres*—Blockade of sympathetic preganglionic ...s with a local anesthetic as they emerge from the cord by ( ) total ...al block, (b) epidural block, ( ) sympathetic ganglion block Total ...al or epidural block feasible and used Sympathetic ganglion block ...practical.

UNCHANGED INITIALLY BY BLOCKADE, DECREASED LATE

Blood Volume—Decreased by withdrawal of blood from radial (artery) Objectionable because innervation remains intact and induces vasoconstriction. May lapse into irreversible shock.

PHYSIOLOGICAL CHANGES DURING DELIBERATELY INDUCED HYPOTENSION

Brain—Cortex depressed. Psychometric tests indicate cerebral changes postoperatively. Quantity of anesthetic reduced as blood pressure falls. Cerebral oxygen consumption unchanged (unanesthetized). Decreases with anesthesia. A.V difference widened. Intracranial pressure reduced. Brain volume decreased (arteriotomy). Cerebral blood flow decreased. Decreased still more with head-up tilting. Cerebral congestion with head-down tilting. Cerebral damage favored by head-up position.

E.E.G. shows suppression suggestive of anoxia. Depression of high voltage fast activity as pressure declines. Ceases at 80 mm. Hg. Use of vasopressors restores to normotensive state and return of activity t normal.

Vagus—Active during spinal and epidural block. Ganglionic blockade prevents transmission of impulses.

Metabolism—Oxygen consumption decreased 30% or more. Nonvolatile drugs metabolized more slowly during and after hypotension.

Lung—Ventilation decreased. Arterial blood oxygen unchanged. CO_2 tension variable. Tends to increase. Total CO_2 content increases. CO_2 combining power decreased.

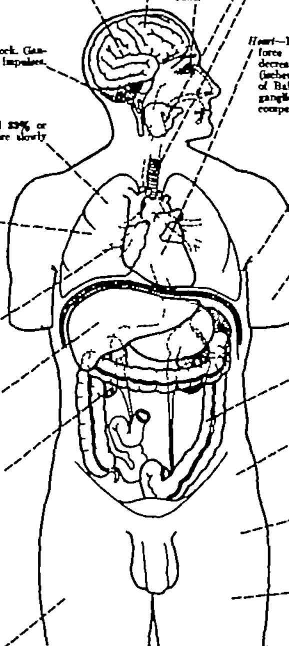
Bronchi—Increased tone—spasm possible (spinal and peridural).

Liver—Dye excretion impaired for as long as 7 days. Occult liver dysfunction enhanced.

Kidney—Renal blood flow and filtration rate depressed. Filtration decreased. Urinary output decreased. Varies with degree of hypotension. Anuria follows if systolic less than 40 mm. Hg is sustained. Clearance of drug decreased during hypotension. Drugs tend to cumulate. Renal dysfunction in post-operative period common. Excretion rate of sodium and water prolonged. Filtration rate remains depressed, even though tension is restored to normal if hypotension exists for more than 2 hours.

Blood—Volume unchanged during blockade unless prolonged. Decreased with arteriotomy. Plasma volume reduced if progresses into irreversible shock.

Blood sugar decreased



Eyes—Pupils dilate. Accommodation lost. Blurred vision due to effect of drug. Blindness postoperatively due to anoxia, mask pressure, or thrombosis of retinal artery.

Salivary Glands—Secretions decreased.

Trachea—Slough of mucosa may occur due to pressure from intratracheal cuffs.

Heart—Depression of myocardium decreases contractile force and mean arterial pressure. Coronary blood flow decreases. E.K.G. changes suggestive of infarct (ischemia). Stroke volume decreased due to activation of Bainbridge reflex (spinal). Pulse increased with ganglionic blockade (vagi blocked). Stroke volume compensated for.

Venous Pressure—Right auricular pressure decreased. Peripheral venous pressure increased. Venous return to heart markedly decreased.

Blood Pressure—Pulse pressure decreased. Diastolic pressure reduced due to decreased peripheral resistance. Systolic must be reduced to 80 mm. Hg to effectively block ooze (both spinal and ganglionic blockade). Blood pressure not changed (early) with arteriotomy. Postural changes: Decreases with head up tilt, increases with head-down tilt.

Gastro-intestinal—Gastric secretions decreased. Bowel constricted (spinal). Dilated (autonomic blockade).

Circulation Time—Prolonged. May be doubled. Blood flow decreased. A.V difference widened (spinal, epidural and systemic denervation).

Arterioles and Capillaries—Capillary pressure not decreased. Arterioles relaxed (except in arteriotomy—constricted). Oozing decreases. Splanchnic blood flow decreased. Digital blood flow increased.

Limb—Negative pressure applied to extremity with plethysmograph. F vors dilatation of vessels and pooling of blood in extremity. Not practical.

Skin—Temperature increased due to vasodilatation. Blood flow increased. Sweating absent. Slough may occur from pressure due to straps, retractors, etc

CONTRAINDICATIONS

(1) Arteriosclerosis of major vessels.

(2) Essential hypertension.

(3) Essential hypotension, or shock from any cause.

(4) Hypovolemia.

(5) Anemias.

(6) Impaired renal function.

(7) Liver dysfunction.

(8) Cardiac diseases with impaired myocardial function.

(9) Polycythemia—thrombi may result.

(10) Adrenal deficiencies.

COMPLICATIONS AND SEQUELAE

(1) Hemorrhage postoperatively due to inadequate hemostasis.

(2) Prolonged cerebral depression postoperatively (anoxia)

(3) Cerebral damage due to inadequate perfusion.

(4) Thrombosis of major vessels, particularly the cerebral, coronary

(5) Oliguria and anuria.

(6) Asystole due to inadequate perfusion.

DISADVANTAGES AND OBJECTIONS

(1) Circulation time prolonged causing A.V difference to be widened—tissue anoxia may result.

(2) Irreversible shock may develop.

(3) Responses to denervation unpredictable. Vary from patient to patient.

TYPES OF SURGERY FOR WHICH EMPLOYED

(1) Neurosurgery

(2) Radical surgery for malignant disease

(3) Fenestration, nephrolithotomy and other procedure requiring a dry field for success.

DRUGS USED

Trimethaphan Camphorsulphonate (Arfonad)—0.1–0.2 mgm. per pound. Administered as continuous intravenous drip composed of 1 mgm. per cc. Administered over a period of 10 minutes until blood pressure is reduced to 80 mm. Hg and then adjusted to drip at rate to maintain tension at desired level.

Pentamethonium and Hexamethonium—Hexamethonium preferred. Dose varies from 5–25 mgm. intravenously in fractions. Both drugs characterized by tachyphylaxis. Prolonged effect in some patients. Difficult to reverse.

Anesthetic Technique—"Controlled" hypotension may be induced during any type of anesthesia—nitrous oxide-ether, nitrous oxide-thiopental succinyl choline, cyclopropane, cyclopropane-ether, etc.

ADVANTAGES OF GANGLIONIC BLOCKADE OVER OTHER METHODS

(1) Greater controllability

(2) Reversal possible with ephedrine, phenylephrine and other vasopressors. Response to adrenergic substances remains intact.

(3) May be interrupted with greater ease (with short-acting drugs)

ARTERIOTOMY

Description—Blood drawn from radial artery into sterile receptacle with heparin. Re-infused later. Oozing diminished by vasoconstriction.

Objections

(1) Peripheral resistance increased. No vascular denervation

(2) Irreversible shock may occur

(3) Artery sacrificed—gangrene of hand possible.

(4) Blood cannot be re-infused in toto due to contracted vascular bed.

(5) Relatively complicated and time consuming.

PRECAUTIONS

(1) Limit period of hypotension to one hour or less—irreversible shock may develop otherwise.

(2) Avoid pressure on exposed parts of body—necrosis may develop.

(3) Induce and maintain hypotension until need for it is no longer present (tachyphylaxis to drug may develop—subsequent doses without effect)

(4) Restore blood pressure to normotensive level at conclusion of operation—visualize bleeding points.

(5) Replace blood as lost.

HYPOTHERMIA

HISTORY—First observed by Walther in rabbits in 1862. Reported by Britton in 1922. Temple Fay (*Philadelphia*) cooled narcotized patients for treatment of cancer. McQuiston advocated cooling during surgery in 1947. James Arnolt (Aberdeen, 1847) used cooling for surgery.

DEFINITIONS

TOTAL BODY HYPOTHERMIA—The deliberate reduction of total body temperature accomplished by inactivation of the heat regulating temperature by a central nervous system depressant (any volatile anesthetic or non-volatile basal narcotic) and exposing the body to cold environment (water bath, cold air, etc.) just above freezing temperatures. *Used for reducing general metabolism of the tissues. Inactivation of heat control mechanisms converts the subject from a homothermal one to a poikilothermal.*

HIBERNATION—The voluntary inactivation of the heat regulating center by an animal endowed with this ability so that body temperature may be reduced to decrease metabolism. This inactivation is quickly and voluntarily reversible.

ARTIFICIAL HIBERNATION—The inactivation of the heat regulating center in a non-hibernating animal by drugs (phenothiazines) and reduction in body temperature by loss of heat to the environment. Temperature reduction comparatively slight. Non-reversible by the animal.

REGIONAL COOLING—The cooling to low temperatures of an organ (brain) vulnerable to ischemia during occlusion of the circulation by cooling blood entering that organ.

HYPERTHERMIC ANESTHESIA—The regional cooling of a limb by occluding the blood supply and surrounding limb in ice. Designed to obtain anesthesia by cold. Used for "physiological" amputation.

PURPOSES OF TOTAL BODY COOLING

(1) Reduces metabolism of tissues in procedures in which ischemia is anticipated.

(2) Reduces cerebral volume in neurosurgical procedures.

(3) Reduces body temperature in hyperpyrexia.

(4) Reduces blood pressure—possibly protects against hemorrhagic shock.

DISADVANTAGES AND HAZARDS

1. Cardiac irritability increased. Irreversible ventricular fibrillation may occur.
2. Respiratory acidosis occurs.
3. Uncontrollable lag may cause cooling to lethal range.
4. Tissue damage may occur from pressure, freezing with supercooled ice or heat on re-warming.
5. Re-warming slow and difficult.
6. Depression of circulatory system persists beyond restoration of normal temperature.
7. Heat regulatory mechanism remains unstable for periods of time after re-warming.
8. Cumbersome, awkward, time-consuming.
9. Reactionary hemorrhage may occur postoperatively.

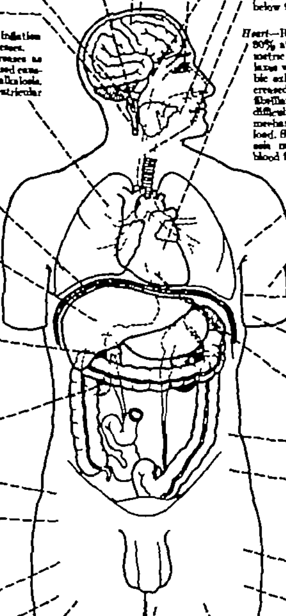
METHODS OF COOLING

1. Total body immersion in cold water
   (a) Cooling uniform and rapid
   (b) *Least controllable, cumbersome*
   (c) Cooling must be accomplished before patient is positioned.
2. Application of icebags.
   ( ) *Slow but most controllable*
   (b) Least reliable
   (c) *Fat necrosis reported most often with this*
3. Surrounding body with blankets containing coils through which ice water flows
   ( ) Slow
   (b) Skin burns on re-warming
   ( ) *Reasonably controllable*
4. Air cooling by placing cold air in chamber
   (a) Cumbersome
   (b) Slow
   (c) *Frostbite most common by this method*
5. Pleural peritoneal perfusion with saline.
   ( ) Slow
   (b) Cumbersome
   (c) Awkward
   (d) Large volumes of solutions needed
6. Gastric or colonic lavage with ice water
   ( ) Cumbersome
   (b) *Not controllable*
7. Removing blood cooling and returning to body
   ( ) Complicated
   (b) Not readily available
   ( ) Contamination possible
   (d) Hemolysis
8. Use of drugs alone (phenothiazines)
   (a) Temperature falls slowly
   (b) Not controllable
   (c) Extreme low temperatures not obtainable
9. Regional cooling. Extremity packed in ice for 2-3 hours. Used for hypothermic anesthesia for surgical procedures or to reduce metabolism in limb.

REWARMING

Spontaneous rewarming occurs at 1°C. per hour average. Reflexes appear at 31°—consciousness at 33°C. Quicker with surface warming. Temperature may overshoot and continue to rise above normal.

Cardiac output fails to return to normal after rewarming. Blood pressure returns to normal at normothermia. Circulatory derangements ( ) overcome the longer period of cooling. Tend to become restless with rewarming.


Cortex—Planes and stages of Guedel nullified below 30°C. Loss of consciousness at 29 C. Returns at 31 34° (without anesthesia) Below 28°C. no anesthetic agent is required. E.E.G shows progressive decrease of activity
Heat Regulating Center—Must be inactivated by drugs to produce cooling Hibernating animals voluntarily restore center to activity Non-hibernation animals unable to do so.
Respiratory Center—Depressed. Inactivated at 23°C. Artificial respiration required. Thiopental causes respiratory arrest before circulatory Ether stimulates locally Apnea does not result before cardiac arrest.
Carotid Body—Activity decreased.
Lungs—Respiratory rate slowed. Deflation and inflation prolonged and more difficult as cooling progresses. Quantities of gases dissolved in blood increases as temperature is lowered. Dissolved CO_2 increased causing acidosis. Hyperventilation may cause alkalosis. Sudden release of CO_2 may predispose to ventricular fibrillation.
Metabolism—Heat output decreases 40 cal./sq. mm. body surface 37°C.; 10 t 25°C.; 6 at 22°C. Oxygen consumption decreased. Increased in shivering. Normothermic persons remove 4% oxygen from inspired air Hypothermic at 25° about 2%.
Liver—Chemical reactions slowed. Reduced activity of enzymes. Hepatotoxic effect of some drugs enhanced (vinyl ether) Drugs slowly metabolized. Onset and duration may be prolonged.
Adrenals—Corticoid output decreased. Response to surgery delayed and diminished but not completely suppressed. Secretion of epinephrine and norepinephrine reduced. Adrenal response to A.C.T.H. not decreased. Glomerular filtration and renal blood flow decreased.
Kidney—Decrease in urinary output which is proportional to decrease in blood flow Return to normal t normothermia. Does not prevent renal damage from ischemia of kidney caused by occluding renal artery Distal tubular function reduced and eliminated at 22°C. Proximal tubular activity little affected
Deep Reflexes—Disappear at 25°C., reappear at 31°C.
Muscles—Usually spastic in flexion Responds to relaxants. Shivering occurs in surface cooling when narcosis is insufficient to depress heat regulating center Increases oxygen consumption 400% and cardiac activity
Nerve—Conduction decreased below 25°C and ceases at 4°C.
Body Temperature—Continues to drift after surface cooling is terminated.
Subcutaneous Fat—Necrosis possible at site of pressure due t straps, retractors, etc Adipose tissue tends t solidify Children have it more than adults More oleic acid in adult (liquid) than newborn More palmitic (solid) in newborn
Cerebrospinal Fluid Pressure—F lls with body temperature. Rises during induction of anesthesia, intubation or during shivering.
Eye—Pupils dilated. Ability to perceive light disappears at 27°C. Corneal reflex disappears at 21°C.
Ear—Hearing disappears at 27°C. Control of equilibrium disappears at approximately 27°C.
Pharynx—Pharyngeal reflex obtunded below 25°C.
Larynx—Necrosis of mucous membrane may result from pressure of cuffed intratracheal tube Reflex abolished below 25°C.
Heart—Rate decreases. Cardiac output decreased at 80% at 25°C. Systolic time increased. Time for isometric relaxation increased. Heart contracts and relaxes with more completeness. Cooling inhibits aerobic oxidation of metabolites. Cardiac irrit bility increased progressively as temperature falls. Ventricular fibrillation occurs at 25°-20°C. Electric defibrillation difficult without rewarming. Fibrillation initiated by mechanical stimulation. Not precipitated by over load. Sudden increase in pH from rapid relief of acidosis may cause ventricular fibrillation. Coronary blood flow not decreased.
Circulation Time—Prolonged, almost doubled.
Blood Pressure—Difficult to determine by auscultatory technique due to intense vasospasm. Decreases progressively with cooling. Returns to normal with rewarming.
Venous Pressure—Variable Decreases after rewarming
Peripheral Resistance—Increased up to 25%. Use of general anesthesia tends t decrease vasoconstriction.
Oesophagus—Oesophageal temperatures more accurate index of cardiac temperature than rectal.
Blood *Volume*—Decreased. Plasma volume decreased by transudation of fluid into tissue spaces.
Blood—Viscosity increased. Thrombocytopenia and an increase in W.B.C. during. Increase in W.B C afterward. Hemorrhage of magnitude tolerated during normothermia may be fatal. Eosinophils increase Replace blood as it is lost.
Bleeding Time—Prolonged. Decrease in platelets may be factor
Clotting *Time*—Prolonged. Alterations in fibrinogen content may be factor
Plasma Volume—Diminished about 10%. Plasma trapped in some of small vessels. Plasma protein not changed.
Skin—Cherry red color during—pale during rewarming—lips and mucous membranes blue. Necrosis may occur due to pressure on ischemic areas. Freezing point—0·1

COMPLICATIONS AND ACCIDENTS DURING ANESTHESIA

Convulsions—Causes not definitely established. May accompany anoxia, CO_2 excess or both, or follow accidental intravenous administration or overdosage of local anesthetic. Idiopathic type usually occurs if fever, acidosis, and particularly if CO_2 excess are present. Cause not known—many theories to explain it—pyrexia, increased cerebral vascularity, hypocalcemia, hypoglycemia, ketosis, atropine overdosage, alkalosis, impurities in drugs, cerebral edema, sepsis, neurotoxin, etc. None proved. May be due to direct stimulation of motor centers by drug (vinethene)

Dilated Pupil—Overdosage of anesthetic drugs, anoxia, excessive atropine or scopolamine

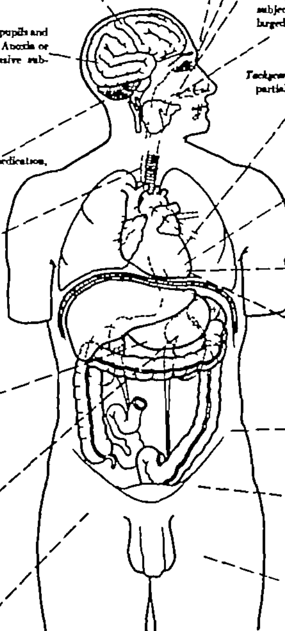
Unequal Pupils—Undetermined, sign of cerebrovascular accident

Salivation—Premedication administered too early, late, or insufficient in quantity

Status Lymphaticus—Sudden death of unknown origin; subjects have hyperplasia of lymphoid tissue or enlarged thymus seen in young subjects.

"*Cerebral Accident*"—Signs variable: unequal pupils and flaccid paralysis most common symptoms. Anoxia or hypercapnia may precipitate in hypertensive subjects.

Tachycardia—Shock, blood loss, excessive atropine or partial respiratory obstruction may be cause



Bradycardia—Usually caused by drug, anoxia or heart block due to pre-existing disease

Prolonged Second Stage—Unsatisfactory premedication, chronic alcoholism, respiratory obstruction

Arrhythmias—May occur with all types of agents and procedures. Most frequent with cyclopropane and chloroform; may decrease cardiac output which predisposes to cardiac failure

Vagal Reflexes—Elicited by stimulation of hilus of lung, trachea or esophagus. Results in apnea, cardiac arrhythmias and hyper- or hypotension

Ventricular Fibrillation—Results from increased cardiac irritability induced by agents such as cyclopropane. Increased sympathetic activity and adrenalin output may enhance irritability

Vomiting—Occurs during induction or maintenance if patient passes into stage II. Full stomach and changes of position predispose

Asystole—Anoxia, overdosage with failure to revive, or vagal reflexes.

Hypotension—Follows spinal anesthesia, blood loss, trauma, reflex stimulation, postural changes, overdosage, incompatible blood.

Regurgitation—Occurs during deep anesthesia. Common when gastric dilatation or intestinal obstruction are present. May cause drowning

Hypertension—May be caused by hypercapnia (from exhausted soda lime; large dead space or added CO_2), specific effect of anesthetic agent; vasoconstrictor drug in local anesthetic solutions. Reflex stimulation, or excitement during induction.

Sweating—Warm environment, respiratory obstruction, prolonged ether anesthesia

Respiratory Failure—May be caused by overdose of agent, over-premedication, central effect of anoxia on medullary center; paralysis from overdose of local anesthetic. May follow circulatory failure from shock due to trauma, blood loss or neurogenic origin.

Epistaxis—Trauma from nasal airways is most frequent cause.

Aspiration—The presence of vomitus, blood, pus, lymphoid tissue instruments, loose teeth, etc. in the airway may lodge in trachea and bronchi. Secretions or blood in thoracic surgery passes from pathological secretions portion to healthy portion.

Apnea—May be caused by:

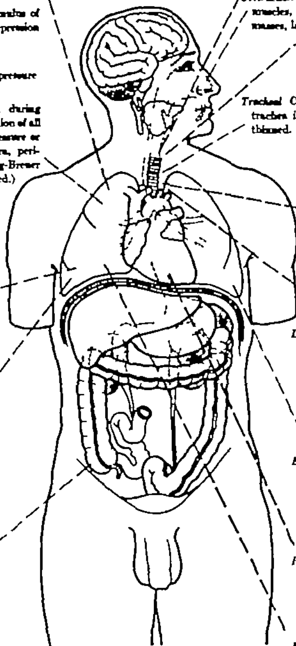
(1) Oxygenation and removal of anoxic stimulus of carotid body in cases of respiratory depression from overmedation.

(2) Overdistention of alveoli from positive pressure.

(3) Apprehensive subject may hyperventilate during second stage causing acapnia or combination of all three factors. Increased intra-cranial pressure or reflex stimulation of periosteum, pleura, peritoneum or bronchi stimulation of Hering-Breuer reflex may cause it. (Overdosage excepted.)

Obstruction—Due to relaxation of tongue pharyngeal muscles, secretions, compression of airway tumor masses, laryngeal spasm, etc.

Tracheal Collapse—Occurs in pathological states of trachea in which tracheal cartilages are eroded or thinned.



Coughing—Occurs during light anesthesia, also following intubation. Abdominal contents may be pushed outward causing technical difficulties. May be induced by hilar stimulation.

Hyperpnea—Hypercapnia due to local alveolar stimulation caused by agent, awkward position, or other compensatory response to hyperventilation.

Laryngeal Spasm—Due to many causes—CO_2 excess, excessive secretions or canister dust, reflex stimulation, high concentration of agent, manipulations with laryngoscope, central stimulation (cyclo or pentothal).

Dyspnea—Anoxia, CO_2 excess, awkward positions, central depression of respiratory center.

Bronchospasm—Presence of catheter in trachea. Central effect of agent, histamine-like action (of curare) hilar stimulation.

Emboli—

(1) *Air*—not related to anesthesia may occur in thoracic surgery or when large veins are opened (place head below shoulders).

(2) *Fat*—seen after manipulations of traumatized large bones after 2nd to 21st day.

(3) *True embolus*—unusual due to clots being dislodged and carried to pulmonary vessels.

Hiccoughs—May follow manipulations of phrenic nerve diaphragm or CO_2 excess.

Pulmonary Edema—Caused by cardiac decompensation during anesthesia. May be initiated by Trendelenburg position in impending cardiac decompensation or cardiac failure from shock or overdosage, or excessive administration of fluid.

COMPLICATIONS AND ACCIDENTS DURING ANESTHESIA

Convulsions—Causes not definitely established. May accompany anoxia, CO_2 excess or both, or follow accidental intravenous administration or overdosage of local anesthetic. Idiopathic type usually occurs if fever, acidosis, and particularly if CO_2 excess are present. Cause not known—many theories to explain it—pyrexia, increased cerebral vascularity, hypocalcemia, hypoglycemia, ketosis, atropine overdosage, alkalosis, impurities in drugs, cerebral edema, acapnia, neurotoxin, etc. None proved. May be due to direct stimulation of motor centers by drug (vinethene).

Dilated Pupil—Overdosage of anesthetic drugs, anoxia, excessive atropine or scopolamine.

Unequal Pupils—Undetermined; sign of cerebrovascular accident.

Salivation—Premedication administered too early, late or insufficient in quantity.

Status Lymphaticus—Sudden death of unknown origin; subjects have hyperplasia of lymphoid tissue or enlarged thymus; seen in young subjects.

"Cerebral Accident"—Signs variable; unequal pupils and flaccid paralysis most common symptoms. Anoxia or hypercapnia may precipitate in hypertensive subjects.

Tachycardia—Shock, blood loss, excessive atropine or partial respiratory obstruction may be cause.

Prolonged Second Stage—Unsatisfactory premedication, chronic alcoholism, respiratory obstruction.

Bradycardia—Usually caused by drug, anoxia or heart block due to pre-existing disease.

Arrhythmias—May occur with all types of agents and procedures. Most frequent with cyclopropane and chloroform; may decrease cardiac output which predisposes to cardiac failure.

Vagal Reflexes—Elicited by stimulation of hilus of lung, trachea or esophagus. Results in apnea, cardiac arrhythmias and hyper- or hypotension.

Ventricular Fibrillation—Results from increased cardiac irritability induced by agents such as cyclopropane. Increased sympathetic activity and adrenalin output may enhance irritability.

Vomiting—Occurs during induction or maintenance if patient passes into stage II. Full stomach and changes of position predispose.

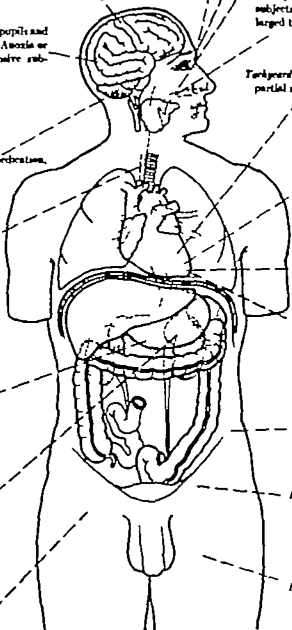
Asystole—Anoxia, overdosage with failure to revive, or vagal reflexes.

Hypotension—Follows spinal anesthesia, blood loss, trauma, reflex stimulation, postural changes, overdosage, incompatible blood.

Regurgitation—Occurs during deep anesthesia. Common when gastric dilatation or intestinal obstructions are present. May cause drowning.

Hypertension—May be caused by hypercapnia (from exhausted soda lime; large dead space or added CO_2), specific effect of anesthetic agent, vasoconstrictor drug in local anesthetic solutions. Reflex stimulation, or excitement during induction.

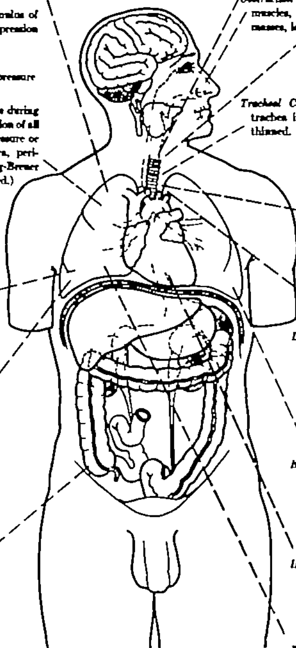
Sweating—Warm environment, respiratory obstruction, prolonged ether anesthesia.



Respiratory Failure—May be caused by overdose of agent, over-premedication central effect of noxia on medullary center paralysis from overdose of local anesthetic May follow circulatory failure from shock due t trauma, blood loss or neurogenic origin.

Epistaxis—Trauma from nasal airway is most frequent cause

Aspiration—The presence of vomitus, blood, pus, lymphoid tumor instruments, loose teeth, etc. In the airway may lodge in trachea and bronchi. Secretions or blood in thoracic surgery passes from pathological secretions portion to healthy portion.



Apnea—May be caused by

(1) Oxygenation and removal of anoxic stimulus of carotid body in cases of respiratory depression from oversedation.

(2) Overdistention of alveoli from positive pressure

(3) Apprehensive subject may hyperventilate during second stage causing acapnia or combination of all three factors. Increased intra-cranial pressure or reflex stimulation of periosteum, pleura, peritoneum or bronchi, stimulation of Hering-Breuer reflex may cause it. (Overdosage excepted.)

Hyperpnea—Hypercapnia due t local alveolar stimulation caused by agent, wkward position, or other compensatory response to hyperventilation.

Dyspnea—Anoxia, CO_2 excess, wkward position, central depression of respiratory center.

Emboli—

(1) *Air*—not related to anesthesia may occur in thoracic surgery or when large veins are opened (place head below shoulders)

(2) *Fat*—seen after manipulations of traumatized large bones after 2nd to 21st day

(3) *True embolus*—unusual due to clots being dislodged and carried t pulmonary vessels.

Obstruction—Due to relaxation of tongue pharyngeal muscles, secretions, compression of airway tumor masses, laryngeal spasm, etc.

Tracheal Collapse—Occurs in pathological states of trachea in which tracheal cartilages are eroded or thinned.

Coughing—Occurs during light anesthesia, also following intubation. Abdominal contents may be pushed outward causing technical difficulties. May be induced by hilar stimulation

Laryngeal Spasm—Due to many causes—CO_2 excess, excessive secretions or canister dust, reflex stimulation, high concentration of agent, manipulations with laryngoscope, central stimulation (cyclo or pentothal)

Bronchospasm—Presence of catheter in trachea. Central effect of agent, histamine-like action (of curare), hilar stimulation.

Hiccoughs—May follow manipulations of phrenic nerve diaphragm or CO_2 excess.

Pulmonary Edema—Caused by cardiac decompensation during anesthesia. May be initiated by Trendelenburg position in impending cardiac decompensation or cardiac failure from shock or overdosage, or excessive administration of fluid.

POST ANESTHETIC SEQUELAE

Vasomotor Center—May be depressed by excess of non-volatile drugs.

Respiratory Center—May be depressed by non-volatile drugs administered in excess or from cumulative action.

Vomiting Center—Emesis and nausea common. May be due to anoxia during anesthesia, effect of agent, circulatory disturbances or surgical manipulations.

Lungs—Atelectasis may follow within first 48 hours. Relationship to anesthesia not established. Broncho-pneumonia may follow aspiration. Lung abscess may follow aspiration. Emboli (air, fat or clot) may occur. Not related to anesthesia. Pulmonary edema may occur. Relationship to anesthesia doubtful.

Diaphragm—Hiccoughs may occur. Relationship to anesthesia not established.

Liver—Hepatitis follows use of halogenated hydrocarbons in small percentage of cases. Latent period precedes onset of condition.

Kidney—Renal damage uncommon when kidney is not diseased. Oliguria frequent, anuria not common.

Bladder—Atony and urinary retention frequent.

Proctitis—Caused by irritation from avertin, rectal ether and other rectal anesthetics.

Wound—Evisceration may follow coughing from respiratory complication.

Wound Infections—Rarely caused by hematoma from increased ooze due to drug.

Body Temperature—Hyperthermia result from cerebral damage from anoxia. Heat stroke or unknown cause.

Nerves—Palsies may follow spinal anesthesia, particularly 6th and 6th nerves.

Cortex—Damage from anoxia or hypercapnia during anesthesia may cause twitchings, convulsions or other neuromuscular symptoms. Coma and death may follow severe cases.

Eye—Conjunctivitis caused by allowing ether and other volatile liquids or secretions to pass into the eye.

Trachea—Tracheitis usually follows intubations.

Pharynx—Pharyngitis may follow trauma caused by airways or suction tips.

Heart—Anesthetics rarely cause any notable effects after withdrawal of drug.

Stomach—Gastritis may follow use of irritating drugs. Gastric dilatation may occur. Relationship to anesthesia not known.

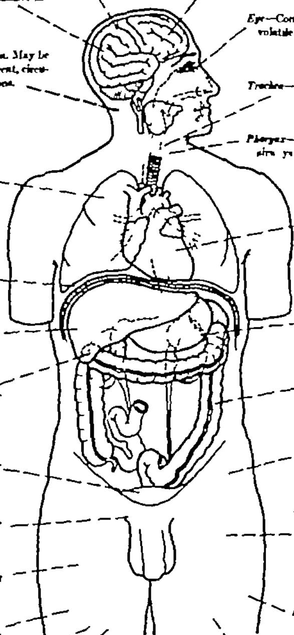
Intestines—Distention and even ileus may occur. May be caused by anesthetic partly and postoperative sedation.

Veins—Thrombosis follows intravenous administration of concentrated solutions.

Blood—Hemoconcentration frequent from dehydration or shock. Acidosis and hyperglycemia occur from anesthesia when metabolic disturbances and renal diseases are present.

Extremities—Gangrene may be caused by use of vasoconstrictors with local anesthetics in vasospastic diseases. Also use of highly concentrated solution of drugs.

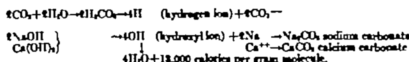
Skin—Irritating drugs produce erythema. Rashes often follow use of non-volatile drugs. Subcutaneous emphysema may occur after forceful ventilation of lung or after explosions, due to trauma of respiratory tract. Slough may follow use of locally irritating anesthetic drugs, oily solutions, or extravasation of barbiturates.



THE CHEMICAL ABSORPTION OF CARBON DIOXIDE

HISTORY—First applied to anesthesia by Dennis Jackson in 1915 on animals, also in man (St. Louis, Mo.) in a few clinical trials. Ralph M. Waters introduced "to and fro" filter in 1923. Brian Sword and Richard Von Foregger introduced "circle filter" in 1926. Benedict in 1909 used soda lime for carbon dioxide absorption in studies on metabolism. Wilson and Dewey developed granulated soda lime for use in inhaler in 1919.

PRINCIPLE—The exhaled atmosphere containing carbon dioxide is passed through a filter containing alkaline substances. Carbonic acid forms from interaction of carbon dioxide and water which is in turn neutralized by the alkali to form carbonates, water and heat.



$2CO_2+2H_2O \rightarrow 2H_2CO_3 \rightarrow 4H$ (hydrogen ion) $+ 2CO_3^{--}$

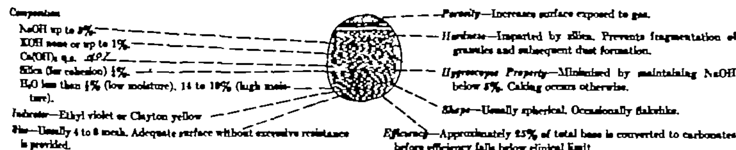
$\left.\begin{matrix} 2NaOH \\ Ca(OH)_2 \end{matrix}\right\} \rightarrow 4OH$ (hydroxyl ion) $+ 2Na \rightarrow Na_2CO_3$ sodium carbonate

$Ca^{++} \rightarrow CaCO_3$ calcium carbonate

$4H_2O + 13{,}000$ calories per gram molecule.

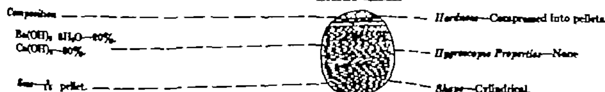
ABSORBENTS—Two absorbents are in current use—soda lime and bara lime (baralyme). Soda lime for anesthesia is a specially prepared mixture of sodium and calcium hydroxides to conform to requirements of hardness, size and porosity and moisture content for clinical use. Specimens vary according to manufacturers. Bara lime is composed of barium and calcium hydroxide. Soda lime for anesthesia possesses the following features:

SODA LIME



The sodium hydroxide is the more active of the two bases. It imparts greater efficiency to the mixture than would be possessed by the lime alone. The bulk of the absorption is carried out by the calcium hydroxide. One pound absorbs for six hours intermittent use at 200 cc. CO_2 output per minute.

BARA LIME



Barium hydroxide and calcium hydroxide are moulded and compressed into pellets. The barium hydroxide is more active and soluble than the calcium and serves as the activator. One pound lasts six to eight hours intermittent use.

APPARATUS—Two types—to and fro and circle type inhalors are currently used. Both are satisfactory. They possess the following features, advantages and disadvantages.

ADVANTAGES OF CARBON DIOXIDE ABSORPTION

1. Allows inhalation of warmed gases and vapors—conserves heat.
2. Allows little or no fluctuation in depth of anesthesia.
3. Encloses flammable mixtures.
4. Allows use of high oxygen tensions.
5. Allows use of positive pressure.
6. Economical.
7. Mitigates against water loss through lungs.

DISADVANTAGES OF CARBON DIOXIDE ABSORPTION

1. Increases complexity of apparatus for administration of inhalation anesthesia.
2. Possibility of inhaling alkaline dust.
3. Absorbent—may act as a catalyst and decompose agents—may favor explosions.
4. Excessive heat may be generated by chemical reaction.

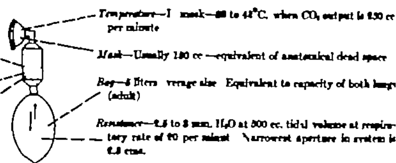
TO AND FRO—Consists of a mask attached to a cylindrical canister and breathing bag. During expiration gases pass from mask to canister to bag; during inspiration direction is reversed. A closely fitting mask allows complete rebreathing of all gases. Metabolic oxygen requirement must be added.

FEATURES

Canister—Must accommodate tidal volume of patient in the inter- and intragranular spaces for efficient absorption.

Size—8 × 13 cms. Accommodates 500 gm. 4 to 8 mesh soda lime. Has an intergranular and intragranular air space of 425 cc.

Material—Metal preferred for stability and to help dissipate heat.



Advantages of To and Fro Filter

(1) Apparatus close to head and accessible for controlled breathing.
(2) Gases pass over absorbent twice yielding more efficient absorption.
(3) Inspired air is warm.
(4) Minimal resistance. No valves or long tubings.
(5) Apparatus simple. Absence of mechanical parts which may become deranged.

Disadvantages of To and Fro Filter

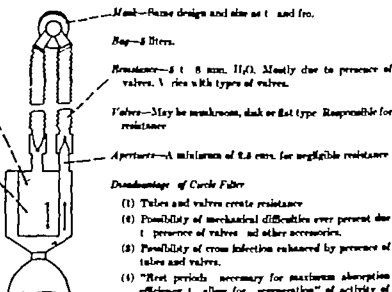
(1) Proximity to face favors inhalation of alkaline dust.
(2) Proximity to face may cause excessively hot gases to be inhaled.
(3) Dead space from lips to mask becomes progressively greater as absorbent is exhausted.
(4) Efficiency reduced if air space in canister does not equal tidal volume.
(5) Difficult to approximate and hold on face.

CIRCLE FILTER—An inhaler composed of a mask, bag and canister. A valve at the inlet and outlet of the canister permits only a unidirectional flow of gases. Two corrugated tubes approximately 30" long connect the mask to the canister.

FEATURES

Canister—Inter- and intragranular air space must equal or be greater than tidal volume of patient for optimum efficiency. May be greater but efficiency falls if air space is less than tidal volume.

Temperature—Varies usually 29 to 31 C. in mask at 250 cc. CO_2 output per minute at 25°C. (45 to 48°C. in canister)



Advantages of Circle Filter

(1) Inspired gases cooler than in to and fro (29 to 31°C.).
(2) Possibility of inhaling dust minimized by long tubing.
(3) Easier to manipulate—canister is placed away from face.
(4) Absorption equally as efficient as to and fro.
(5) Less "dead space" in tubes from mask to filter than in to and fro.

Disadvantages of Circle Filter

(1) Tubes and valves create resistance.
(2) Possibility of mechanical difficulties ever present due to presence of valves and other accessories.
(3) Possibility of cross infection enhanced by presence of tubes and valves.
(4) "Rest periods" necessary for maximum absorption efficiency to allow for "regeneration" of activity of soda lime.

REGENERATION OF ACTIVITY—Sodium carbonate and calcium carbonate form when carbonic acid neutralizes the hydroxides, the former preferentially. Sodium carbonate is soluble, calcium carbonate totally insoluble. Interaction of soluble sodium carbonate with unused calcium hydroxide still present in partially exhausted granule yields insoluble calcium carbonate and regenerates sodium hydroxide which reactivates the absorbent.

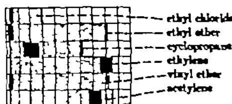


$$Na_2CO_3 + Ca(OH)_2 \rightarrow 2NaOH + CaCO_3 \downarrow$$

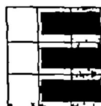
FIRES AND EXPLOSIONS

PREDISPOSING FACTORS

1. *Inflammable Materials*—Most anesthetic drugs burn readily. They contain C, H and O. Halogens tend to decrease inflammability. Concentrations of agents required for anesthesia (black areas) fall within explosive limits (shaded areas).



2. *Oxygen Supply*—Limits of oxygen concentration required for combustion with anesthetic agent (black) less than physiological requirements (shaded). The more intimate the mixture the more rapid the combustion and usually the more destructive the response.





Ether in beaker burns. Only one layer of molecules can combine with oxygen.



Equal amount of ether vaporized explodes. All molecules combine with oxygen at same time. Steam and expanding CO_2 form.

3. *Ignition Source*—Ignition temperature varies with mixture and material; some mixtures require longer period of contact with ignition temperature to self-sustain combustion than others. The higher the flash point, the safer the compound. In anesthesia, the ignition source may be inadvertently provided by

Flames	*Electricity*	*Static Electricity*	*Miscellaneous*
Pipes	Motors	Friction from motions of	Spontaneous combustion
Cigarettes	Heaters	people	Oil on oxygen or air valves
Gas and	X-rays	gases	under pressure
Alcohol lamps	Cauteries	parts of equipment	
	Poor switches	blankets	
	Endoscopes	bags	
	High frequency units	tables	
		adhesive removal	

4. *Miscellaneous Factors*—Size and shape of containers and pressures of vapors or gases cause inflammability to vary. Propagation in horizontal direction greater than vertical. Dilution with inert gases (CO_2, N_2, He etc.) lowers limits of inflammability because these gases possess a high heat capacity or high rate of heat conduction.

PREVENTIVE PROCEDURES

1. Provide closed system—high humidity (65% discharges static).
2. Provide adequate ventilation to dilute and diffuse vapors.
3. Wash apparatus with inert gas after each use. Rinse with water.
4. Use pure agents—ether peroxides have low ignition temperatures.
5. Avoid sudden movements of personnel, clicking of metals, and friction.
6. Use spark proof electrical equipment. Avoid cautery and high frequency circuits.
7. Provide intercoupling—interconnecting apparatus, operator and patient with high resistance (of 1 megohm) allows slow discharge of highly charged body and prevents sparks.
8. Provide conductive rubber.
9. Eliminate sources of static electricity—woolen blankets, nylon and silk clothes, rubber soled shoes.

GLOSSARY

Absolute zero — (0°A.) 273° below 0°C. At this temperature molecular motion is believed to cease

Absorption — Passage of a substance into the interior of another by solution or penetration.

Acapnia — Decrease of carbon dioxide tension in blood below that required to maintain stimulation of the respiratory center

Acarbia — Reduction of blood carbonates and bicarbonates below normal.

Acid — A substance which yields hydrogen ions (H^+) in solution. Really a substance which yields oxonium (H_3O^+) in aqueous solution.

Acid anhydride — *A non-metal oxide which reacts with water to form an acid.*

Acid salt. — A salt containing one or more replaceable hydrogen atoms ($NaHCO_3$)

Action potential — Current produced during physiological activity of nerve or other tissue

Activate — To induce a state of increased chemical activity

Activated charcoal — Charcoal treated to increase its absorptive power

Acyclic — An open chain compound possessing no ring formation.

Acyl group — An organic radical having the configuration $R-\overset{\overset{O}{\|}}{C}-$

Additive effect. — Effect caused by simultaneous administration of two similar drugs represented by arithmetical average

Addiction — Physical dependance to a drug resulting in the abstinence syndrome upon withdrawal. Organic symptoms and manifestations follow

Adsorption — A process believed to be physical in nature in which molecules of a gas or liquid condense or adhere as a film, on the surface of another substance.

Agent (anesthetic) — Term used by anesthetists to designate an anesthetic drug.

Airway — Pathway for inspired air from lips and nostrils to alveoli.

Alcohol — An organic compound, derived from a hydrocarbon, containing one or more hydroxyl (OH) groups.

Aldehyde — An organic compound, derived from a hydrocarbon, containing $-\overset{\overset{O}{\|}}{C}-H$ group

Aliphatic — *Open-chain, organic compounds.*

Alkali — A strong, water soluble base

Alkaloid — Physiologically active substance derived from plants, usually having a complex chemical structure containing nitrogen, and possessing basic properties. (Names usually end with "ine")

Alkyl — Radical derived from an aliphatic hydrocarbon, produced by removing one hydrogen from it. A radical cannot exist alone as such ($-CH_3$ methyl)

Allotropy — The ability of certain elements to exist in more than one form, due to a particular arrangement of the atoms or molecules.

Amalgam — An alloy composed of mercury and one or more metals. The metal dissolves in the mercury

Amaroid — A bitter principle obtained from a plant.

Amide — Ammonia with one hydrogen replaced by an acyl group $R-\underset{\underset{NH_2}{|}}{C}=O$

Amine — Substance produced by replacing one or more hydrogen atoms of ammonia by alkyl or aromatic, alicyclic or heterocyclic radicals. $R-NH_2$—primary; R_2NH—secondary; R_3N—tertiary

Amorphous — A substance which does not have or does not appear to have a crystalline structure

Amphoteric substance — A substance which possesses radicals which exhibit both acidic and basic properties $COOH-R-NH_2$.

Anesthetic index — $\dfrac{\text{No. units of anesthetic required for anesthesia}}{\text{No. units of anesthetic required for respiratory failure}}$

Angstrom unit — 10^{-8} cm., a hundred millionth of a centimeter

Anhydride — The residue after the elements of water are abstracted from an acid or a base

Anhydrous substance — A substance free from water

Anion — A negatively charged ion which is attracted to the anode (electrode where oxidation occurs) Cl^- Br^- CO_3

Antagonism — Opposing action of one drug by another (negative summation)

Aromatic — Group of compounds derived from benzene and related hydrocarbons.

Association — The union of simple similar molecules to form complex molecules. Such a union is reversible and remains incomplete $X(H_2O) \rightarrow (H_2O)_x$

Atom — The smallest unit of an element which takes part in the formation of a compound. An atom is a positive nucleus surrounded by electrons

Atomic number — The net positive charge on the nucleus. This represents the number assigned to the atom in the periodic table

Atomic weight — The weight of an atom compared to the weight of an oxygen atom taken as 16.000.

A-V difference — Difference in volumes per cent between content O_2 of arterial and venous blood.

Avogadro's hypothesis — Hypothesis stating that at the same temperature and pressure equal volumes of gases contain the same number of molecules.

Avogadro's number — The number of molecules in a gram-molecule (mole) 6.06×10^{23}

Base	(1) A hydroxide of a metal which yields hydroxyl ions in solution and neutralizes an acid to form a salt and water (2) A substance capable of combining with proton.
Basic anhydride	The oxide of a metal which forms a base when it reacts with water
Basic salt	A salt containing replaceable or hydroxyl groups.
Binary compound	A compound whose molecule is composed of two elements.
Boiling point	The temperature at which the vapor pressure within a liquid equals atmospheric pressure.
Brownian movement	The random agitation of particles of matter of molecular magnitude produced by collision of molecules.
Calorie	The amount of heat required to raise the temperature of one gram of water from 14°C. to 15°C. The large calorie which is used in nutrition equals 1000 calories.
Calorimeter	An apparatus used to measure the amount of heat liberated or absorbed during a chemical or physical reaction.
Carbonyl.	C=O group, characteristic of ketones but also present in other radicals.
Carboxyl.	O ‖ —C—OH group, characteristic of organic acids.
Catalysis	The change in the rate of a chemical reaction induced by the presence of a substance (called catalyst) which is itself unchanged after the reaction is completed.
Cathode	(1) The negative electrode of an electrolytic cell. (2) The electrode where reduction occurs.
Cation.	A positively charged ion which migrates to the cathode in electrolysis.
Chemical equilibrium	The stat of balance between two chemical reactions proceeding at equal rates but in opposite direction, each undoing the work of the other
Complex ion	Ions produced by the union of a number of simple ions, or by the union of a simple ion with molecules.
Complex salt	A salt which contains complex ions.
Compound substance	A substance which can be decomposed int recognized elements.
Conjugation	Addition of a new group by a biochemical mechanism to a chemical substance which changes its physiological activity (glycine and benzoic acid—hippuric acid)
Covalent molecule	A molecule in which the bond between two atoms is a shared electron pair such as H Cl, H H, Cl Cl.
"Cracking"	A process in which hydrocarbons of high molecular weight are broken down into smaller molecules by the aid of heat and pressure.
Critical pressure	The minimum pressure required to liquefy a gas at the critical temperature
Critical temperature	The temperature above which a gas cannot be liquefied regardless of the pressure used
Crystalloid	A material which when dispersed in a dispersion medium forms a true solution.
Cyclic	Closed-chain chemical compound (cyclopropane)
Degradation	A disintegration of a chain of carbon atoms in a stepwise manner
Density	Mass per unit volume, e.g., grams per cubic centimeter
Depression	Decrease of power of cells to function.
Derivative	The resultant of a chemical reaction.
Detonator	Flame, fuse, shock or other agent which causes an explosive mixture t explode
Dextrorotatory	Rotating a plane of polarized light to the right.
Dibasic acid	Acid with two replaceable hydrogen atoms in its molecule.
Diffusion	(1) Passage of molecules through membranes (such as in alveoli; (2) The spreading apart of molecules of gases or fluids.
Distillate	The vapor which condenses and is caught in the receiver of a distillation apparatus.
Dissociation.	Reversible decomposition of complex molecules into simpler molecules.
Dissolve	The dispersion of one material into another so that an apparently homogeneous mixture forms. There may or may not be chemical alteration.
Dose	Toxic—Amount of drug which causes untoward symptoms in the verage individual (also fatal dose) Minimum Lethal (M.L.D.$_{50}$) The amount of drug fatal to 50% of the animals in controlled experimental conditions. Minimal—Smallest amount of a drug which has therapeutic effects. Maximal—Largest amount of drug which can be tolerated without toxic symptoms. Therapeutic—Dose lying somewhere between maximal and minimal.
Double salt	A salt in which two atoms of a metal are combined with one acid radical or one atom of a metal is combined with two acids.
Drug	A chemical agent which affects living protoplasm.
Dyne	The force necessary t impart to a mass of one gram an acceleration of one centimeter per second per second.
Efflorescent substance	A substance which loses water of crystallization when exposed to air e.g., $Na_2CO_3 10H_2O \rightarrow Na_2CO_3 H_2O + 9H_2O$
Electron	The unit of negative electricity which possesses mass equivalent to 1/1845 of the hydrogen atom.
Elementary substance	One of small group of substances of nearly complete stability whose chemical properties give each of them a definite place in the Periodic Table.
Emulsion	A dispersion in which the dispersed phase is a liquid and dispersion medium is a liquid.
Endogenous	Arising from sources within the organism.
Endothermic	Reaction absorbing heat.
End point	The completion of a reaction usually evident by the first perceptible alteration of the color of an added indicator

Enzyme	A substance elaborated by living cells which possess catalytic properties.
Epoxy	A group which has the structure O —C— C— | |
Equilibrium	*A state of balance between t opposing forces or processes.*
Exogenous	Arising from without the organism or system.
Exothermic	Reaction accompanied by the evolution of heat.
Explosive mixture	Mixture capable of extremely rapid or almost instantaneous combustion, the expansive force of which is destructive
Extract	Concentrated preparation of animal or vegetable drug obtained by solution from source and concentrating preparation to prescribed standard.
Fermentation	A chemical reaction accomplished by living cells t liberat energy anaerobically aided by enzymes.
Flash point	Lowest temperature t which vapors of a liquid may be ignited by a flame
Fluid extract	Liquid preparation of vegetable drug containing alcohol as solvent or preservative Each cc contains therapeutic constituent of 1 gm. standard drug it represents.
Fluorescence	A process in which light is bsorbed and is instantaneously re-emitted with altered frequency
Foam	A dispersion in which the dispersed phase is gas and the dispersion medium is a liquid
Fractional distillation	The process by which two or more liquids of different boiling points are separated by distillation and each fraction, as it forms, is collected in separate containers.
Glycoside	Neutral principle containing a carbohydrat molecule in conjunction with one or more chemical bodies.
Gram atom	Atomic weight of an element expressed in grams
Gram molecule	The molecular eight of an element or compound expressed in grams.
Habituation	A condition characterized by "psychic craving" hich follow continued use of drug.
Halide	A substance composed of a radical and one or more halogen toms.
Halogens	The elements fluorine chlorine bromine and iodine
Heat of dissociation	The heat (expressed in calories) expended in the dissociation of one mole of a substance into specified products.
Heat of formation	The heat in calories hich is absorbed or liberated during the reaction in which a mole of compound forms from the necessary elements.
Heat of vaporization	Heat in calories required t h nge a unit weight of liquid to the vapor state at a given temperature
Heterocyclic	Cyclic structure containing other elements beside carbon in the ring
Humidity (absolute)	The amount of w ter vapor present per unit volume of gas or air when saturated at given temperature
Humidity (relative)	The actual amount of water vapor present in the air or a gas divided by the amount necessary for saturation at the same temperature and pressure expressed in per cent.
Hydrogenation	Process of adding hydrogen (t an unsaturated compound)
Hydrate	A crystalline substance containing definit proportion of chemically combined w ter
Hydrolysis	Reaction between the ions of salt and those of w ter t form an acid and base one or both of which is only slightly dissociated.
Hydrous	Combined with an indefinit or variable amount of water
Hygroscopic	A substance which absorbs moisture from the tmosphere
Hyperbaric	Specific gravity of a solution hich is greater than that of spinal fluid
Hypobaric	Specific gravity of a solution less than that of spinal fluid.
Idiosyncrasy	Abnormal or unusual response t drug even t extremely small doses.
Indicator	A substance capable of undergoing a color change t definite hydrogen ion (or other specific ion) concentration.
Induction	Period from start of anesthesia t attainment of third stage
Inert element	An lement located n the zero group of the Periodic Table
Interface phase	The surface which separates two phases e.g. oil w ter
Ion	A atom or group of atoms bearing positive or negative charge
Ionization	The formation of ions by interaction of a substance ith solvent.
Isoelectric point	The pH t which an emulsoid colloid exhibits minimum of swelling and may be nearly precipitated.
Iso	A prefix placed before the name of an aliphatic compound indicati g branching of the chain.
Isobaric	A solution having the same specific gravity spinal fluid
Isomerism	Stat in hich tw compounds have the same composition but different molecular structures.
Isomers	Molecules composed of the same number and types of toms but which are arranged differently withi the molecule
Isotopes	Atoms which possess the same atomic umber but slightly different tomic eights due to differences in number of particles in the nuclei U ually possess almost identical chemical properties.
Latent heat	The quantity of heat expressed in calories which is absorbed or liberated when mole of substance changes from one stat to another at fixed temperature e.g. conversion of 18 g of ice to water at 0°C. requires 1440 calories of heat or 80 calories per gram

Latent heat of vaporization	The amount of heat in calories required to change unit mass of a substance existing in a liquid form at a given temperature into a vapor without change of temperature. The heat of vaporization for water at 100°C. is approximately 536 calories per gram.
Law Le Chatelier's	If external factors such as temperature and pressure disturb a system in equilibrium adjustment occurs in such a way that the effect of the disturbing factors is reduced to a minimum.
Levorotatory	Rotating the plane of polarized light to left.
Lipophilic	Showing marked attraction or solubility in lipoids.
Macerate	The process of softening a solid by steeping it in a liquid.
Margin of safety	Margin between the therapeutic dose and lethal dose
Melting or freezing point.	The temperature at which the solid and liquid phases of any pure substance are in equilibrium.
Mercaptan	An alcohol in which sulphur replaces oxygen in the hydroxyl group to form an (SH) group
Metamer	A chemical compound which resembles another in properties but differs from it in structure and composition.
Molal	A solution in which one gram-molecular weight of solut is dissolved in one thousand grams of solvent.
Molar solution	A solution which contains one mole of solute per liter of solution.
Mole	The molecular weight of a substance expressed in grams.
Molecular weight	The sum of the atomic weights of all the atoms in a molecule.
Monobasic acid.	An acid having one replaceable hydrogen atom in its molecule
N	Refers t Nitrogen—A radical is attached to nitrogen in a compound. N-methyl means a methyl group attached to the nitrogen atom.
n	Normal—Refers to straight-chain compound n-propane.
Nascent	The stat of an element at the instant it is liberated from a compound.
Neutral principle	Drugs obtained from plant or animal sources which are neutral in reaction (names end with "in")
Neutralization	Union of hydrogen and hydroxyl ions to form undissociated molecules of water
Normal solution	A solution containing an active reagent which may replace unite with, liberate, or cause to react with one gram of hydrogen per liter
Occlusion	The process by which large volumes of gases are absorbed by solids.
Oxidation	(1) The combination of oxygen with other elements to form oxides. (2) The process in which an element gains electrons.
Oxidation potential	The measure of the tendency of a substance to be oxidized to some specified other substance, under specified conditions.
Oxonium ion	The ion H_3O^+ formed by direct union of a proton with water The oxonium ion forms when an acid dissolves in water The old concept was that hydrogen (H) ion was formed.
Oxygen capacity (vol. %)	Maximum amount of oxygen a given volume of blood absorbs when equilibrated with an excess of oxygen expressed in cc. per 100 cc.
Oxygen content (vol. %)	Oxygen in volumes per cent present in blood at given moment.
Oxygen saturation	Oxygen content divided by oxygen capacity expressed in volumes per cent.
Paralysis	Cessation of cell function.
Periodic table	A table of the elements, arranged in rows and columns. The different columns represent different groups of chemically similar elements.
pH	Concentration of hydrogen ions expressed as the logarithm of the reciprocal of the concentration.
Pharmacodynamics	The study of the action of drugs on the living organism.
Pharmacotherapeutics	Study of drugs and use in relation t treatment of disease
Pharmacognosy	Study of physical characteristics of crude drugs.
Pharmacy	Art of preparing, compounding, and dispensing drugs and medicines.
Phase	A homogeneous portion of matter which is distinct in composition and properties from other phases in contact with it.
Plane	Level or "stratum of third stage anesthesia
Polymer	A new compound formed by the combination of several molecules of a substance. The compound has a percentage composition the same as the initial compounds but the molecular weight is a multiple of the initial compound.
Polymorphism	The ability of substance to exist in two or more crystalline forms.
Potentiation	Addition of one drug, not necessarily possessing similar action, to another to increase its action.
Precipitate	An insoluble solid substance which forms from chemical reactions between solutions.
Pressure	The force exerted against a unit area usually expressed in dynes or grams per square centimeter or in pounds per square inch.
Proton	A positively charged hydrogen atom, H which is identical with the hydrogen nucleus.
Qualitative test	A test which attempts to identify a material or the ingredients of a mixture
Quantitative test	A test used to determine the actual amount of a given substance in a mixture or compound.
Racemic	A mixture of equal portions of a dextro and a levo compound. There is no rotation of the plane of polarized light.
Radical	A group of atoms capable of acting as single elements in chemical reactions (CO_3''; SO_4''; PO_4'''; etc)

Radioactive — Refers to a substance capable of a continuous discharge of invisible rays, which affect the photographic plate the electroscope or produce a visible fog in moist air

Reactivity — Possessing the tendency toward entering into a specified chemical reaction.

Rectify — Purification of a substance by fractional distillation.

Reduction — Removal of oxygen addition of hydrogen gain of electrons.

Reducing agent — (1) A substance capable of removing oxygen from another substance (2) A substance which contains an atom which donates one or more electrons.

Replacement series — An arrangement in which the metals are listed in order of their decreasing chemical activity

Reversible reaction — A reaction which under proper conditions can progress in both directions at one time

Saponification — The hydrolysis of fats and oils by alkalis and water to form soaps and alcohols.

Saturated solution — A solution in which an equilibrium exists between undissolved solute and dissolved solute.

Saturated vapor — This condition is present when the space above a liquid contains all the vapor it can acquire and hold at the given temperature and which is in equilibrium with the liquid.

Solute — The substance which dissolves in a solvent.

Solvent — The constituent of a solution which does the dissolving and is present in greater amounts than the solute

Specific gravity (gases) — The ratio of the weight of one liter of gas compared to the weight of one liter of air

Specific gravity (solid or liquid) — The ratio of the weight of a unit volume of a substance to the weight of an equivalent volume of water

Specific heat — The heat required to raise the temperature of one gram of a substance from 14–15°C.

Spectrum — The separation of light into its component parts by the aid of a prism or grating.

Stable — A term applied to a substance which has no tendency to decompose spontaneously

Stability (as applied to compounds) — The property of being able to resist being decomposed or chemically altered.

Standard conditions — 0°C. and 1 atmosphere pressure (760 mm. Hg)

Standard atmospheric pressure — The pressure caused by the weight of the atmosphere at sea-level. It is a pressure of 1033 grams per square centimeter or 14.9 pounds per square inch. It elevates mercury in barometer to a height of 760 mm.

Stimulation — Increased functioning of protoplasm induced by some extracellular substance or agent.

Strong acid — An acid which is completely ionized in aqueous solution.

Sublimation — The transformation of solid to a vapor without its passing through the liquid state

Supercooling — The cooling of a liquid below its freezing point, without freezing occurring

Summation — The combined action of two drugs given simultaneously equal the algebraic sum of their individual effects.

Surface tension — Contraction force of a surface usually expressed in dynes per square centimeter

Suspension — A dispersion in which the dispersed phase is composed of a solid.

Syneresis — Spontaneous shrinkage of a gel, accompanied by slow separation of liquid.

Synergism — Production of an effect by two drugs possessing similar action acting together which is greater than the sum of each if they act alone (positive summation)

Tension — Pressure of a gas.

Ternary compound — A compound whose molecule is composed of three elements.

Thio — Prefix indicating sulphur-containing compound.

Tincture — Alcoholic solution of a drug Usually contains 10 grams of crude drug per 100 cc. of solution.

Titration — The measurement of the volume of liquid needed to complet a given chemical reaction.

Tolerance — The need to progressively increase a dose of a drug to maintain given therapeutic response with repeated administration.

Cross tolerance—Resistance to action of given drug results in tolerance to a chemically related drug possessing similar action.

Individual—Tolerance to a drug which a subject has never received before

Species—Insensitivity species exhibits to particular drug.

Tribasic acid — An acid containing three replaceable hydrogen atoms in each molecule

Valence — (1) The number of atoms of hydrogen (or equivalent elements) which combine with, or are replaced by the atom in question. (2) Polar valence is the excess of positive or negative charges on an atom or radical. (3) Non-polar valence is the number referring to electron pairs shared with other atoms

Vapor density — The ratio of the weight of gas or vapor to the weight of an equal volume of hydrogen measured under the same conditions of temperature and pressure

Vapor pressure — The partial pressure exerted by vapor

Viscosity — Resistance to flow of fluids due to the internal friction of the liquid.

Volumes per cent — (Blood) cc of gas liberated from 100 cc. of liquid.

Water of hydration — The water contained in a hydrate

Weak acid — An acid which is only slightly ionized in aqueous solution.

ATOMIC WEIGHTS

Element	*Symbol*	*Exact Weight*	*Approximate Weight*
Argon	A	18	18
Barium	Ba	137.36	137
Bromine	Br	79.916	80
Calcium	Ca	40.08	40
Carbon	C	12.01	12
Chlorine	Cl	35.45	35
Copper	Cu	63.57	63
Fluorine	F	19.00	19
Helium	He	4.003	4
Hydrogen	H	1.008	1
Iodine	I	126.92	127
Iron	Fe	55.84	56
Lithium	Li	6.94	7
Mercury	Hg	200.61	201
Neon	Ne	20.18	20
Nitrogen	N	14.008	14
Oxygen	O	16.00	16
Phosphorus	P	31.02	31
Potassium	K	39.00	39
Sodium	Na	22.997	23
Sulphur	S	32.06	32
Zinc	Zn	65.38	65

CONVERSION FACTORS FOR METRIC SYSTEM

	Exact	*Approximate*
1 cubic centimeter	16.23 minims	16 minims
1 liter (1000 cc.)	33.8 fl. oz.	1 qt.
1 milligram	0.0154 grain	1/60 gr.
1 gram	15.432 grains	15 gr.
1 grain	64.8 milligrams	64 mgm.
1 dram	3.88 grams	4 gm. or 4 cc.
1 ounce	28.35 grams	30 gm. or 30 cc.
1 millimeter	—	1/25 inch
1 inch	2.54 cm.	2.5 cm.
1 pint (16 oz.)	473.00 cc.	500 cc.

TEMPERATURE CONVERSION FACTORS

Fahrenheit to Centigrade—Subtract 32 from F. reading and multiply by 5/9.
Centigrade to Fahrenheit—Multiply C. by 9/5 and add 32 to the result.

Drug	*Infiltration*	*Intraspinal*
Local anesthetics		
alypin hydrochloride	.5–2%	
apothesine hydrochloride	5–2%	2 cc of a 4% solution
diothane hydrochloride	2%	
larocaine hydrochloride	25–2%	
metycaine hydrochloride	5–1%	
supercaine hydrochloride	1/1000 solution up to 100 cc	15–20 cc. of 1/1500 solution in .5% saline (Jones')
pontocaine hydrochloride		15–20 mgm.
procaine hydrochloride	.5–1%	100–150 mgm.

QUALITATIVE TESTS

Peroxides in ether

Potassium iodide (10%) 2 cc
Ether 5 cc

Shake stoppered, keep in dark place 20–30 minutes. Yellow color in ether layer indicates presence of peroxides—sensitive to .0005% peroxide

Aldehydes in ether

Nessler's solution 2 cc.
Ether 20 cc.

Immediate yellow color or precipitate indicates presence of aldehydes. Test positive if mixture stands, due to oxidation of alcohol in the ether

Barbiturates in urine

Extract urine (acidified) with 10 volumes of chloroform per unit volume.

Chloroform extract 1 cc.
Isopropyl amine 5% in absolute methyl alcohol 0.6 cc.
Cobaltous acetate (1%) in absolute methyl alcohol 0.1 cc
Reddish violet color indicates positive reaction.

REFERENCES

GENERAL ARTICLES

Adriani	*The Chemistry of Anesthesia.* Springfield, Thomas, 1945. Chemistry
Adriani and Rovenstine	*Anesthesiology,* 4 253, 1943. Effects on Bronchi.
Adriani and Rovenstine	*Am. J. Physiol.,* 135:102, 1941 Anesthetics on Bronchial Tonus.
Barbour	*Am. J. Surg.* 34 153, 1936 General Pharmacology
Barbour	*Anesthesiology,* 1 121 1940. Water Exchange
Barbour and Bourne	*Am. J. Physiol.,* 67 399, 1923. Heat Regulation.
Barcroft and Rothschild	*Arch. de Pharmacol. et de Therap.,* 38 440 1930. Splenic Volume and Anesthesia.
Bastedo	*Materia Medica, Pharmacology and Therapeutics.* Philadelphia, Saunders and Co., 1932.
Beecher	*Physiology of Anesthesia.* London, Oxford Univ. Press, 1938.
Bisaini	*Anesth. and Analg. (Italian),* 2:518, 1934. Bromides.
Bloor	*J. Biol. Chem.,* 19 13, 1914. Blood Fat.
Bolliger	*J. Biol. Chem.,* 69 721, 1926. Phosphate Metabolism.
Bollman	*Proc. Staff Meet., Mayo Clin.,* 4:200 1929 Liver and Anesthesia.
Bonnycastle	*J. Pharmacol. & Exper. Therap.,* 75 18, 1942. Anesthetics.
Bourne	*Brit. M.J.* 2:706, 1932. Liver and Anesthesia.
Bourne and Stehle	*J.A.M.A.,* 83:117 1924 Phosphoric Acid in Anesthesia.
Boyd	*Canad. M.A.J.* 34 150, 1936. Leukocytosis and Anesthesia.
Boyd	*Surg. Gynec. & Obst.,* 62 677 1936. Anesthesia and Blood Lipoids.
Brown and Wardell	*Ohio Chem. Co. Bull.,* 118 Explosions.
Bulow	*Biochem. J.,* 27 1832, 1933 Brain Oxidation and Narcotic Gases
Burge	*Am. J. Physiol.,* 69 304, 1924. Catalase and Oxygen Consumption.
Burge, Wickwire et al.	*Anesth. and Analg.* 15 261, 1936. Cortical Brain Potential.
Campbell and Morgan	*J. Pharmacol. & Exper. Therap.,* 49 456, 1933. Hyperglycemia.
Case and Stiles	*Anesthesiology,* 7 29 1946. Positions and Vital Capacity
Chamberlain	*Textbook of Organic Chemistry.* Philadelphia, Blakiston's, 1934. Topic on Chemistry
Comroe and Schmidt	*Am. J. Physiol.* 121 75, 1938. Carotid Body
Coryllos and Birnbaum	*Am. J. M. Sc.* 183:317 1932. Gases in the Lungs.
Cushny, Grollman and Slaughter	*Textbook of Pharmacology and Therapeutics* 12th Ed. Philadelphia, Lea and Febiger 1940.
Collen	*Anesthesia for the General Practitioner* 3rd Ed. Chicago, Year Book Publishers, 1951
Dallemagne	*Anesth. and Analg.* 15 82, 1936. Acid-base in Anesthesia.
Dalton, et al.	*Proc. Soc. Exper. Biol. & Med.,* 23 961, 1930 Kidney
Derbyshire et al.	*Am. J. Physiol.* 116 577 1936 Action Potentials of Cortex.
Dooley and Wells	*Am. J. Physiol.,* 90:250, 1929. Reflexes.
Eadie	*J. Biol. Chem.,* 146 85, 1942. Cholinesterase
Emerson	*Anesth. and Analg.* 17 100 1938. Adrenalin.
Ernst	*Arch. Int. Pharmacol.* 58:208, 1938. Ciliary Activity
Farson, Carr and Krantz	*Proc. Soc. Exper. Biol. & Med.,* 61:70, 1946. Steroid Anesthesia.
Finesinger and Cobb	*J. Pharmacol. & Exper. Therap.,* 53:1 1935. Cerebral Circulation.
Fleischmann and Rand	*J. Gen. Physiol.,* 17 791 1933, 1934. Red Blood Cells.
Ferguson	*Anesthesiology,* 4 392, 1943 Skin Temperature
Gonzales, Vance and Halpern	*Legal Medicine and Toxicology* New York, Appleton-Century 1937
Guedel	*J.A.M.A.,* 83 1736, 1924. Metabolism.
Guedel	*Inhalation Anesthesia.* New York, Macmillan, 1937
Gwathmey	*Anesthesia* 2nd Ed. New York, Macmillan, 1924
Haas	*Science* 46 462, 1917 Respiration.
Henderson	*Canad. M.A.J.* 17 1159, 1927 Toxicity
Henderson and Haggard	*Am. Chem. Soc. Monographs,* 2nd Ed. 1927 Noxious Gases.
Hewer	*Recent Advances in Anesthesia and Analgesia* Philadelphia, Blakiston, 1939.
Hoff	*New England J. Med.* 217 579, 1937 Ether Versus Chloroform.
Hoopers	*Arch. Surg.* 26 909 1933 Cholesterol and Glycemia
Howard, Babcock and Adriani	*Anesthesiology,* 10 131 1949 Uterine Motility
Isenberger	*Proc. Staff Meet. Mayo Clin.* 4 254, 1929 Minute Volume Respiration.
Jacobs and Parpart	*Biol. Bull.* 62 313, 1932 Erythrocyte Permeability
Jones	*Proc. Am. Soc. Anesth.* Oct. 1938 Explosions.
Knoefel	*Anesth. and Analg.* 15 137 1936 Effects on Sympathetic Nervous System.
Kurtz, Bennett and Shapiro	*J.A.M.A.* 106 434, 1936 E.K.G. During Anesthesia
Larson, Smith, et al.	*J. Pharmacol. & Exper. Therap.* 82 133, 1944 Carotid Body
Leigh	*Anesthesiology,* 2 419 1941 Acid Base Balance
Lerman	*Arch. Int. Pharmacol.* 51 304, 1936 Glucose and anesthesia.

Lucas — *Anesth. and Analg* 13 206, 1934 Ciliary Activity
MacNider — *Surg Gynec & Obst* 40 493, 1928. General Effects.
McDowell — *Brit. M J* 1 690 1935 Anesthesia and Shock.
May — *Chemistry of Synthetic Drugs*, London, Longmans, Green & Co., 3rd Ed., 1921
Meek — *Physiol. Rev* 21 324 1941 Anesthesia on Heart.
Meek, Hathaway and Orth — *J Pharmacol.*, 61 240, 1937 Cardiac Rhythm.
Mengle — *Arch. Surg* 34 830, 1937 Anesthesia and Lymphatic Absorption.
Miller — *J Pharmacol. & Exper Therap.*, 23 147 1924; 27 41 1926 Intestinal Activity
Modern Hospital — 43 84 1934 Explosions.
Murphy and Young — *J Physiol.*, 76 395, 1932. Liver Glycogen.
Mushin — *Physics for the Anesthetist*. Springfield, Thomas, 1947
Ney — *Anesth and Analg* 7 28, 1928. Intracranial Pressure
Pharmacopeia of U.S. — *XIII Chemistry and Official Requirements*
Quastel and Wheatley — *Proc. Roy Soc* 112 60 1932. Brain Oxidation and Narcosis.
Rabinowitch — *Brit. J Exper Path* 8 313, 1927 Blood Coagulation.
Robbins — *J Pharmacol. & Exper Therap.*, 54 426, 1935 Salivary Secretions.
Rucker — *Anesth and Analg* 5 233, 1926 Anesthetics and Uterine Contractions.
Rydin — *C r Soc. d Biol.*, 93 654 1925 Anesthetics and Sympathetic Drugs.
Seevers, DeFazio and Evans — *J Pharmacol. & Exper Therap.*, 53 90, 1935 Diffusion of Gases.
Seevers — *Ann. Rev Physiol Am. Physiol. Soc.*, 1 489, 1939 General and Local Anesthesia.
Seevers and Waters — *Phys Rev* 18 447 1938 Pharmacology of Anesthetic Gases.
Selris and Rose — *Anesthesiology*, 5 580 1944 Effect on Heart Beat.
Smith and Van Liere — *J Pharmacol. & Exper Therap.*, 63 84 1938. G I Movements.
Smith — *Physiology of the Kidney*, London and New York, Oxford University Press, 1937
Sollmann — *Manual of Pharmacology*, Philadelphia, Saunders, 6th Ed 1948.
Taylor and Waters — *Anesth. and Analg* 14 276, 1935 Leukocytosis.
Tha — *Tohoku J Exper Med.*, 31 290, 1937 Sedimentation Time
Van Slyke and Peters — *Quantitative Clinical Chemistry* Baltimore Williams and Wilkins Co Vol. 2, 1931 Biochemical Effects.
Van Liere and Northrup — *Anesthesiology*, 5 207 1944 Effects on Colon.
Walton — *Proc Soc. Exper Biol & Med.*, 29 1974, 1932. Kidney Function.
Webster — *Anesth. and Analg* 8 106, 1929 Red Blood Cells
Woodbury Hamilton and Torpin — *Am J Physiol.*, 121 641 1938. Action of Human Uterus.
Wright — *A Textbook of Physiology*, London, Oxford Univ Press, 6th Ed 1936

THEORIES OF NARCOSIS AND BIOLOGICAL EFFECTS OF DRUGS

Adriani — *Chemistry of Anesthesia*, ch. 21–24, Springfield, Thomas, 1945 General Review
Bancroft — *J Phys. Chem.*, 35 215 1931 Chemistry of Anesthesia.
Barbour — *Anesthesiology* 1 2, 1940. Body Fluids.
Field — *Anesthesiology* 8 113, 1947 Cell Respiration.
Gerard — *Anesthesiology*, 8 453 1947 Cell Metabolism.
Seifriz — *Biol. Bull.*, 39 207 1940. Effects on Protoplasm.
Henderson — *Physiol Rev.*, 10 171, 1930 Theories.
Quastel — *Proc Roy Soc. Med.*, 112 60, 1932. Oxidation.

NITROUS OXIDE

Bennett and Seevers — *J Pharmacol. & Exper Therap.*, 61 459 1937 Effects of Anoxia.
Bloomfield — *Proc. Roy Soc. Med.*, 19 30 1926. Chemistry
Brown, Lucas and Henderson — *J Pharmacol & Exper Therap* 31 269 1927 Pharmacology
Chapman, Arrowood and Beecher — *J Clin Investigation*, 22 871 1943 Nitrous Oxide Analgesia.
Clement — *Anesthesiology*, 7 663, 1946 General Article
Courville — *Medicine* 15 129 1936. Pathology of Asphyxia.
Davidson — *J Pharmacol. & Exper Therap* 25 91, 1925. Pharmacology
Downs — *Ann Surg* 99 974, 1934 Carotid Sinus.
Echols, O'Neal and Slocum — *Anesthesiology* 10 164 1949 Premedication.
Green, Carney et al. — *Arch. Intern Med* 35 378, 1925. Elimination.
Haggard — *J A M A.*, 55 2228, 1910 Pharmacology
Hoover — *J A M A.*, 35 579, 1935 Chemistry
Kelleway — *J Physiol* 53 211 1919 Hyperglycemia and Asphyxia.
Killian and Morris — *Ztschr Exper Med* 79 173, 1931 Blood
Leake and Hertzman — *J A M A.*, 82 1162, 1924 Pharmacology
Leslie — *Arch f Exper Path u Pharmakol.*, 116 167 1926. Pharmacology
Luckhardt and Carter — *J A M A.*, 80 765 1923 Pharmacology

McKesson	*Am. J. Surg.* 34 99, 1920. Technique
Miller	*J. Pharmacol. & Exper. Therap.*, 27 41, 1926. Effects on G.I. Tract.
Orcutt and Seevers	*J. Biol. Chem.*, 117 30, 1937. Chemistry
Orcutt and Waters	*Anesth. and Analg.* 12 43, 1933. Chemistry
Seevers and Waters	*Physiol. Rev.* 18 447, 1938. Pharmacology
Wright and Thompson	*J. Pharmacol. & Exper. Therap.*, 38 417, 1930. Nitrous Oxide on Blood Pressure

HYDROCARBONS

Goldman and Goldman	*Anesth. and Analg.*, 4 411, 1925. Acetylene
Henderson and McDonald	*J. Pharmacol. & Exper. Therap.*, 61 184, 1932. Cyclopropane Derivatives.
Krantz, Carr et al.	*Anesthesiology*, 9:404, 1948. Cyclobutane
Krantz, Carr and Vitcha	*Anesthesiology*, 10:413, 1949. Methyl Cyclobutane
Seevers and Waters	*Phys. Rev.*, 18 447, 1938. Anesthetic Gases.
Stoughton	*J. Pharmacol. & Exper. Therap.*, 48 74, 1936. Butanes and Pentanes.
Virtue	*Anesthesiology*, 10:318, 1949. Cyclopentane

ETHYLENE

Bouckaert	*Arch. Int. de Pharm. et de Therap.*, 31:140, 1925. Pharmacology
Johnson and Ivy	*Am. J. Physiol.*, 73 104, 1926. Intestinal Motility
Leake and Hertzman	*J.A.M.A.*, 82:1162, 1924. Concentration.
Luckhardt and Carter	*J.A.M.A.*, 80 765, 1923. General Pharmacology
Luckhardt and Carter	*J.A.M.A.*, 81 1851, 1923. General Pharmacology
Miller and Plant	*J. Pharmacol. & Exper. Therap.*, 27 117, 1923. Pharmacology
Newman	*J.A.M.A.* 108 461, 1937. Ethylene
Nicloux and Yovanovitch	*C. r. Soc. de Biol.*, 93 1033, 1925. Solubility
Sherman, Swindler and McElroy	*J.A.M.A.*, 88 1785, 1926. Pharmacology

CYCLOPROPANE

Adriani	*Chemistry of Anesthesia*, Springfield, Thomas, 1946. Chemistry
Adriani and Rovenstine	*Proc. Am. Physiol. Soc.*, P. 3 3, 1940. Parasympathetic Action.
Allen, Slocum, et al.	*Anesthesiology*, 6 223, 1945. Arrhythmias.
Allen, Stutzman and Meek	*Anesth. and Analges.* 1 253, 1940. Cyclopropane and Epinephrine
Allen, Stutzman and Meek	*Anesthesiology*, 3 8, 30, 1942. Arrhythmias.
Bourne	*Lancet*, 2 20, 1934. Obstetrics.
Burstein	*Anesthesiology*, 7 113, 1946. Procaine for Arrhythmias.
Burstein	*Proc. Soc. Exper. Biol. & Med.*, 38 890, 1938. Cyclopropane
Dripps	*Anesthesiology*, 8 1, 1947. Cyclopropane Shock.
Fry, Anderson and Kenyon	*J. Pharmacol. & Exper. Therap.*, 65 425, 1939. Blood Chemistry
Guedel	*Anesthesiology*, 1 13, 1940. Technique
Haas, McBee, Hinds and Gleaskenkamp	*Anesth. and Analg.* 16 81, 1937. Chemistry
Henderson and Lucas	*Anesth. and Analg.* 9 1, 1930. Pharmacology
Henderson and Lucas	*Arch. Int. de Pharmacol. et de Therap.*, 37 155, 1930. Metabolism.
J.A.M.A.	*Report of the Council*, 112 1064, 1939
Knight	*Anesth. and Analg.* 15 43, 1936. Obstetrics.
Murphy, Crampton & Meek	*Anesthesiology*, 10 416, 449. Effect of Blood Pressure Rise
Neff and Stiles	*Canad. M.A.J.* 35 56, 1936. Blood Acid-base and Sugar
Orth and Meek	*Anesthesiology*, 21 419, 1941. Barbiturates and Arrhythmias
Ragnsky and Bourne	*Canad. M.A.J.* 31 500, 1934. Liver
Robbins	*Cyclopropane Anesthesia*. Baltimore, Williams and Wilkins, 1940. Pharmacology
Robbins and Baxter	*J. Pharmacol. & Exper. Therap.* 58 415, 1936. Pharmacology
Robbins and Baxter	*J. Pharmacol. & Exper. Therap.* 62:170, 1938. Cardiac Output
Romberger	*J. Indiana M.A.J.* 24 18, 1933. Signs of Anesthesia.
Schackell and Blumenthal	*Anesth. and Analg.* 13 135, 1934. Effect on Lungs.
Seevers, Meek, Rovenstine and Stiles	*J. Pharmacol. & Exper. Therap.* 51 1, 1934. Pharmacology
Stormont, Seevers, et al.	*Anesthesiology*, 3 369, 1942. Acid Base Balance
Stutzman, Allen and Orth	*Anesthesiology*, 6 37, 1945. Cyclopropane, Epinephrine, Procaine
Stutzman, Allen and Meek	*Anesthesiology*, 3 430, 1942. Effect of Ether upon Rhythm.
Stutzman and Pettinga	*Anesthesiology*, 10 274, 1949. Arrhythmias
Taylor	*Anesthesiology*, 6 411, 1946. Clinical Use
Thomas, Greely and Guedel	*Anesthesiology*, 6 411, 1941. Cardiac Arrhythmias
Waters and Schmidt	*J.A.M.A.*, 103 975, 1934. Clinical ...
Youmans, Karstens, et al.	*Anesthesiology*, 3 303, 1942. E... ...etrine

ETHER

Banerji and Reed — *J Physiol* 8:370, 1933. Adrenals and Hyperglycemia.
Barbour and Bourne — *Am. J Physiol.*, 67 399 1923. Heat Regulation.
Bhatia and Burn — *J Physiol.*, 78 257 1933. Sympathetic Nervous System.
Black, Shannon & Krantz — *Anesthesiology* 1 234 1940. Cyprome
Blalock — *Arch. Surg* 14 732, 1927 Cardiac Output.
Blalock — *Surg Gynec. & Obst.*, 46 72, 1928. Cardiac Output.
Bowman and Muntwyler — *Proc. Soc. Exper Biol. & Med.*, 35 557 1937 Ascorbic Acid and Ether Anesthesia.
Bourne — *Anesthesiology*, 590, 1940. Impurities.
Boyd — *Surg. Gynec. & Obst.*, 62 677 1936. Lipoids.
Carr, Krantz, et al. — *Anesthesiology*, 8 53, 1947 Newer Ethers.
Cattell — *Arch. Surg* 6 41 1923. Experimental Traumatic Shock and Ether
Dale and Hadfield — *Lancet*, 1 424, 1923. Anesthetic Properties.
Eastman — *Am. J Obst. & Gynec.*, 31 563, 1936. Fetal Oxygen.
Emerson — *Proc. Soc. Exper Biol. & Med.*, 35:376, 1936. Ether on Intestinal Activity
Evans and Krantz — *Anesthesiology*, 3 414, 1942. Cypreth.
Forbes, McIntosh and Sefton — *Am. J Physiol.*, 40 503, 1916. Effect on Electric Activity of Nerve
Forbes and Miller — *Am. J Physiol.*, 40 148, 1916. Nerve
Forbes and Miller — *Am. J Physiol.*, 62 113, 1922. Central Nervous System.
Forbes and Miller — *Anesth. and Analg.*, 2 182, 1923. Central Nervous System.
Fujii — *Tohoku J Exper Med.*, 6 566, 1925 Adrenals.
Gerschman and Marenzi — *C Soc. de Biol.*, 112 509 1933. Blood Potassium.
Ghose — *J Physiol.*, 77 97 1933. Cholesterol.
Gold and Sussman — *Proc. Soc Exper Biol. & Med.*, 26 3 1928. Pupillary Reactions.
Guedel and Treweek — *Anesth. and Analg* 13 263, 1934 Apnoea.
Haggard — *J Biol. Chem.*, 59 737 1924. Absorption and Elimination.
Haines and Milliken — *J Urol.*, 17 147 1927 Renal Function.
Hawk — *Arch. Int. Med.*, 8 39, 1911 Urine Formation.
Keeton and Ross — *Am. J Physiol.*, 48 146, 1917 Hyperglycemia.
Krantz, et al. — *Anesthesiology*, 3 414 1942. Cypreth.
Krantz, Evans, et al. — *J Pharmacol. & Exper Therap.*, 75 30, 1942. Cyclopropyl Vinyl Ether; *J Pharmacol. & Exper Therap.*, 86 138, 1946. Propyl Methyl Ether
Krantz, Jelliffe, et al. — *Anesthesiology* 5 291, 1944 Irritative Action.
Mallinckrodt — *J Am. Chem. Soc.*, 49 26, 1927 Chemistry
McAllister and Root — *Anesthesiology*, 3 401 1942. Sympathetic Effects.
Nardy and Topley — *J A. Pharmaceutical A.*, 17 10, 1928. Stability
Phillips and Freeman — *Proc. Soc. Exper Biol. & Med* 31 296, 1933. Hyperglycemia.
Pilcher and Sollmann — *J Pharmacol. & Exper Therap.*, 6 401, 1915 Action on Vasomotor Center
Pringle, et al. — *Brit. M J* 2 544, 1905 Renal Function.
Robbins — *Anesth. and Analg* 15 153, 1936. Concentration.
Robbins and Pratt — *J Pharmacol. & Exper Therap.*, 56 205, 1936. Potassium.
Ross and Davis — *Am. J Physiol.*, 53 201, 1920. Effect on Pancreas.
Searles and Essex — *Proc Staff Meet. Mayo Clin.*, 11 481, 1936. Effects on Blood.
Stamenovitch and Petkovitch — *C Soc. de Biol.*, 123 430, 1936. Ammonia.
Stewart and Rogoff — *J Pharmacol. & Exper Therap.*, 15 236, 1920. Adrenals and Ether Hyperglycemia.
Van Slyke, Austin and Cullen — *J Biol. Chem.*, 53 277 1922. Acid-base.
Whitacre and Fisher — *Anesthesiology* 8 113, 1947 Metopryl.
White, Shane and Krantz — *Anesthesiology*, 7 662, 1946. Propyl Methyl Ether

VINYL ETHER

Bourne — *Lancet*, 1 868, 1934. Obstetrics.
Bourne, McDowell and Whyte — *Anesth. and Analg* 16 48, 1937 Blood.
Bourne and Raginsky — *Brit. J Anesth.*, 12 62, 1935 Effects on Liver
Bourne and Sparling — *Anesth and Analg* 14 4, 1935. Pharmacology
Emerson, Klym, Abreu and Phatak — *Anesth. and Analg* 16 88, 1937 Hyperglycemia.
Gelfan and Bell — *J Pharmacol. & Exper Therap.*, 47 1, 1933. Anesthetic Action.
Goldman — *Brit. M J* 2 122, 1936. Method of Administration.
Goldschmidt, Ravdin, et al. — *J.A.M.A.*, 102 21 1934. Experimental and Clinical Studies.
Goldschmidt, Ravdin, Lucke — *J Pharmacol. & Exper Therap* 59 1, 1937 Liver
Jacquot and Quevauviller — *Anesth. and Analg* (French) 3 47 1937 Pharmacology
Jones and Beattie — *Indust and Engin. Chem.*, 26 557 1934. Explosive Properties.
Knoefel, Guedel and Leake — *Proc. Soc. Exper Biol. & Med.*, 29 129, 1931 Anesthetic Properties.
Leake — *J.A.M.A.*, 102 1, 1934 Pharmacology
Leake and Chen — *Proc. Soc. Exper Biol. & Med.*, 28 141 1930. Anesthetic Properties.

McKesson — *Am. J. Surg.* 51 [illegible], 1940. Technique.
Miller — *J. Pharmacol. & Exper. Therap.*, 27 41, 1926. Effects on G.I. Tract.
Orcutt and Seevers — *J. Biol. Chem.*, 117 [illegible], 1937. Chemistry.
Orcutt and Waters — *Anesth. and Analg.* 12 45, 1933. Chemistry.
Seevers and Waters — *Physiol. Rev.* 18 447, 1938. Pharmacology.
Wright and Thompson — *J. Pharmacol. & Exper. Therap.*, [illegible] [illegible], 1930. Nitrous Oxide on Blood Pressure.

HYDROCARBONS

Goldman and Goldman — *Anesth. and Analg.*, 4 211, 1925. Acetylene.
Henderson and McDonald — *J. Pharmacol. & Exper. Therap.*, 61 182, 1937. Cyclopropane Derivatives.
Krantz, Carr et al. — *Anesthesiology*, 9 [illegible], 1948. Cyclobutane.
Krantz, Carr and Vitcha — *Anesthesiology*, 10 [illegible], 1949. Methyl Cyclobutane.
Seevers and Waters — *Phys. Rev.* 18 447, 1938. Anesthetic Gases.
Stoughton — *J. Pharmacol. & Exper. Therap.*, 58 74, 1936. Butanes and Pentanes.
Virtue — *Anesthesiology*, 10 318, 1949. Cyclopentane.

ETHYLENE

Bouckaert — *Arch. Int. de Pharm. et de Therap.* 31 150, 1925. Pharmacology.
Johnson and Ivy — *Am. J. Physiol.*, 77 104, 1926. Intestinal Motility.
Leake and Hertzman — *J.A.M.A.*, 82 1162, 1924. Concentration.
Luckhardt and Carter — *J.A.M.A.*, 80 765, 1923. General Pharmacology.
Luckhardt and Carter — *J.A.M.A.*, 81 1851, 1923. General Pharmacology.
Miller and Plant — *J. Pharmacol. & Exper. Therap.*, 23 147, 1924. Pharmacology.
Newman — *J.A.M.A.* 108 461, 1937. Ethylene.
Nicloux and Yovanovitch — *C. R. Soc. de Biol.* 93 1035, 1925. Solubility.
Sherman, Swindler and McElroy — *J.A.M.A.*, 86 1765, 1926. Pharmacology.

CYCLOPROPANE

Adriani — *Chemistry of Anesthesia*, Springfield, Thomas, 1946. Chemistry.
Adriani and Rovenstine — *Proc. Am. Physiol. Soc. P.* 3 [illegible], 1940. Parasympathetic Action.
Allen, Slocum, et al. — *Anesthesiology*, 6 [illegible], 1945. Arrhythmias.
Allen, Stutzman and Meek — *Anesth. and Analges.*, 1 [illegible], 1940. Cyclopropane and Epinephrine.
Allen, Stutzman and Meek — *Anesthesiology* 3 [illegible], 1942. Arrhythmias.
Bourne — *Lancet*, 2 [illegible], 1934. Obstetrics.
Burstein — *Anesthesiology*, 7 113, 1946. Procaine for Arrhythmias.
Burstein — *Proc. Soc. Exper. Biol. & Med.*, 38 [illegible], 1938. Cyclopropane.
Dripps — *Anesthesiology*, 8 1, 1947. Cyclopropane Shock.
Fay, Andersch and Kenyon — *J. Pharmacol. & Exper. Therap.*, 66 [illegible], 1939. Blood Chemistry.
Guedel — *Anesthesiology*, 1 13, 1940. Technique.
Haas, McBee, Hinds and Gluesenkamp — *Anesth. and Analg.* 16 31, 1937. Chemistry.
Henderson and Lucas — *Anesth. and Analg.* 9 1, 1930. Pharmacology.
Henderson and Lucas — *Arch. Int. de Pharmacol. et de Therap.*, 37 [illegible], 1930. Metabolism.
J.A.M.A. — *Report of the Council*, 112 1064, 1939.
Knight — *Anesth. and Analg.* 15 65, 1936. Obstetrics.
Murphy, Crampton & Meek — *Anesthesiology*, 10 416, 449. Effect of Blood Pressure Rise.
Neff and Stiles — *Canad. M.A.J.* 34 [illegible], 1936. Blood Acid-base and Sugar.
Orth and Meek — *Anesthesiology*, 2 [illegible], 1941. Barbiturates and Arrhythmias.
Rapinsky and Bourne — *Canad. M.A.J.* 31 [illegible], 1934. Liver.
Robbins — *Cyclopropane Anesthesia*. Baltimore, Williams and Wilkins, 1940. Pharmacology.
Robbins and Baxter — *J. Pharmacol. & Exper. Therap.*, 58 [illegible], 1936. Pharmacology.
Robbins and Baxter — *J. Pharmacol. & Exper. Therap.* 62 179, 1938. Cardiac Output.
Romberger — *J. Indiana M.A.J.* 28 10, 1935. Signs of Anesthesia.
Schackell and Blumenthal — *Anesth. and Analg.* 13 185, 1934. Effect on Lungs.
Seevers, Meek, Rovenstine and Stiles — *J. Pharmacol. & Exper. Therap.*, 51 1, 1934. Pharmacology.
Stormont, Seevers, et al. — *Anesthesiology* 3 [illegible], 1942. Acid Base Balance.
Stutzman, Allen and Orth — *Anesthesiology*, 6 [illegible], 1945. Cyclopropane, Epinephrine, Procaine.
Stutzman, Allen and Meek — *Anesthesiology*, 3 [illegible], 1942. Effect of Ether upon Rhythm.
Stutzman and Pettinga — *Anesthesiology*, 10 274, 1949. Arrhythmias.
Taylor — *Anesthesiology*, 2 641, 1946. Clinical Use.
Theines, Greely and Guedel — *Anesthesiology*, 2 611, 1941. Cardiac Arrhythmias.
Waters and Schmidt — *J.A.M.A.*, 103 975, 1934. Clinical Aspects.
Youmans, Karstens, et al. — *Anesthesiology*, 3 [illegible], 1942. Effect upon Intestine.

ETHER

Banerji and Reed	*J Physiol* 78 370, 1933 Adrenals and Hyperglycemia.
Barbour and Bourne	*Am. J Physiol.*, 67 399 1923. Heat Regulation.
Bhatia and Burn	*J Physiol.*, 78 257 1933. Sympathetic Nervous System.
Black, Shannon & Krantz	*Anesthesiology* 1 234, 1940. Cyprome
Blalock	*Arch. Surg.*, 14 732, 1927 Cardiac Output.
Blalock	*Surg Gynec. & Obst.*, 46 72, 1928. Cardiac Output.
Bowman and Muntwyler	*Proc. Soc. Exper Biol. & Med.*, 35 557 1937 Ascorbic Acid and Ether Anesthesia.
Bourne	*Anesthesiology*, [illegible]90, 1946. Impurities.
Boyd	*Surg Gynec. & Obst.*, 63 677 1936. Lipoids.
Carr, Krantz, et al.	*Anesthesiology*, 8 83, 1947 Newer Ethers.
Cattell	*Arch. Surg* 6 41 1923. Experimental Traumatic Shock and Ether
Dale and Hadfield	*Lancet*, 1 424, 1923. Anesthetic Properties.
Eastman	*Am. J Obst. & Gynec.*, 31 563, 1936. Fetal Oxygen.
Emerson	*Proc. Soc. Exper Biol. & Med.*, 35 376, 1936. Ether on Intestinal Activity
Evans and Krantz	*Anesthesiology*, 3 414 1942. Cypreth.
Forbes, McIntosh and Sefton	*Am. J Physiol.*, 40 503, 1916. Effect on Electric Activity of Nerve
Forbes and Miller	*Am J Physiol.*, 40 148, 1916. Nerve.
Forbes and Miller	*Am. J Physiol.*, 62 113, 1922. Central Nervous System.
Forbes and Miller	*Anesth. and Analg* 6 134, 1923. Central Nervous System.
Fujii	*Tohoku J Exper Med.*, 5 406, 1925. Adrenals.
Grochman and Marcus	*C r Soc. de Biol.*, 112:509 1933. Blood Potassium.
Ghose	*J Physiol.*, 77 97 1933 Cholesterol.
Gold and Sommen	*Proc. Soc Exper Biol. & Med.*, 26:2, 1928. Pupillary Reactions.
Guedel and Treweek	*Anesth. and Analg* 13 263, 1934. Apnea.
Haggard	*J Biol. Chem.*, 59 737 1924. Absorption and Elimination.
Haines and Milliken	*J Urol.*, 17 147 1927 Renal Function.
Hawk	*Arch. Int. Med.*, 8:39, 1911. Urine Formation.
Keeton and Ross	*Am. J Physiol.*, 48 146, 1917 Hyperglycemia.
Krantz, et al.	*Anesthesiology* 3 414, 1942. Cypreth.
Krantz, Evans, et al.	*J Pharmacol. & Exper Therap.*, 75 30, 1942. Cyclopropyl Vinyl Ether *J Pharmacol. & Exper Therap.*, 86 138, 1946. Propyl Methyl Ether
Krantz, Jelleffe, et al.	*Anesthesiology*, 5 291 1944. Irritative Action.
Mallinckrodt	*J Am. Chem. Soc.*, 49 96, 1927 Chemistry
McAllister and Root	*Anesthesiology* 3 401 1942. Sympathetic Effects.
Nitardy and Tapley	*J A. Pharmaceutical A.*, 17 10, 1928. Stability
Phillips and Freeman	*Proc. Soc. Exper Biol. & Med.*, 31 296, 1933. Hyperglycemia.
Pilcher and Sollmann	*J Pharmacol. & Exper Therap.*, 6 401, 1915 Action on Vasomotor Center
Pringle, et al	*Brit. M J* 2 542, 1905 Renal Function.
Robbins	*Anesth. and Analg.*, 15 168, 1936. Concentration.
Robbins and Pratt	*J Pharmacol. & Exper Therap.*, 56 205, 1936. Potassium.
Ross and Davis	*Am. J Physiol.*, 51 301, 1920. Effect on Pancreas.
Searles and Essex	*Proc. Staff Meet. Mayo Clin.*, 11 481 1936. Effects on Blood.
Stanoevitch and Petkovitch	*C Soc. de Biol.*, 123 430, 1936 Ammonia.
Stewart and Rogoff	*J Pharmacol. & Exper Therap* 15 236, 1920. Adrenals and Ether Hyperglycemia.
Van Slyke Austin and Cullen	*J Biol. Chem.*, 53 277 1922. Acid-base
Whitacre and Fisher	*Anesthesiology*, 9 113, 1947 Metopryl.
White Shane and Krantz	*Anesthesiology*, 7 663, 1946. Propyl Methyl Ether

VINYL ETHER

Bourne	*Lancet*, 1 [illegible], 1934 Obstetrics.
Bourne McDowell and Whyte	*Anesth. and Analg.*, 16 44, 1937 Blood.
Bourne and Raginsky	*Brit. J Anesth.*, 12 62, 1935 Effects on Liver
Bourne and Sparling	*Anesth. and Analg* 14 4, 1935 Pharmacology
Emerson, Klyza, Abreu and Phatak	*Anesth. and Analg* 16 84, 1937 Hyperglycemia.
Gelfan and Bell	*J Pharmacol. & Exper Therap* 47 1, 1933. Anesthetic Action.
Goldman	*Brit. M J* 2 122, 1936. Method of Administration.
Goldschmidt, Ravdin, et al.	*J.A.M A.*, 102 21, 1934 Experimental and Clinical Studies.
Goldschmidt, Ravdin, Lucke	*J Pharmacol. & Exper Therap.*, 59 1, 1937 Liver
Jacquot and Quevauviller	*Anesth. and Analg.* (French), 3 47 1937 Pharmacology
Jones and Beattie	*Indust and Engin. Chem* 26 557 1934 Explosive Properties.
Knoefel, Guedel and Leake	*Proc Soc Exper Biol. & Med.*, 29 130, 1931. Anesthetic Properties.
Leake	*J A M A* 102 1 1934. Pharmacology
Leake and Chen	*Proc Soc. Exper Biol. & Med.*, 28 151, 1930. Anesthetic Properties.

Leake, Knoefel and Guedel	*J Pharmacol. & Exper Therap* 47 5, 1933. Anesthetic Action.
Lott, Smith and Christiansen	*J Am. Pharmaceut. A.*, 26 205, 1937 Preparation.
Lyons	*J.A.M.A.*, 3 1234 1933 Action on Skin.
Melitor	*J Pharmacol. & Exper Therap.*, 57 274 1936. Pharmacological and Toxicological Properties.
Orth, Meek, et al.	*Anesthesiology* 1 246, 1940 General Pharmacology
Peoples and Phatak	*Proc. Soc. Exper Biol. & Med.*, 32 278, 1934. Effect on Intestinal Muscle.
Ravdin, et al.	*J.A.M.A* 108 1163, 1937 Pharmacology
Ruigh and Major	*J Am Chem. Soc.*, 53 2662, 1931 Chemistry

HALOGENATED HYDROCARBONS

Abreu, Auerbach, et al.	*J Pharmacol. & Exper Therap.*, 80 139, 1944. Halogenated Hydrocarbons.
Abreu and Emerson	*Univ. Colorado, Phar* 1 313, 1934 Unsaturated Derivatives.
Adriani	*The Chemistry of Anesthesia.* Springfield, Thomas, 1945
Bollert, Eichler and Hildebrandt	*Arch. f exper Path. u. Pharmakol* 181 100, 1937 Acetylene
Dudley and Neal	*Food Research*, 7 421 1942. Methyl Bromide
Henderson and MacDonald	*J Pharmacol. & Exper Therap.*, 61 182, 1937 Methyl Cyc opropanes.
Peoples, Abreu and Leake	*J Pharmacol. & Exper Therap.*, 48 284, 1933 Gen. article.
Queries and Minor Notes	*J.A.M.A* 138 391, 1948. Tetrachlorethylene

CHLOROFORM

Beilloe and Chauchard	*C Soc. de Biol.*, 99 306, 1928. Chloroform on Vagus.
Blalock	*Surg Gynec. & Obst.*, 46 72, 1928. Cardiac Output.
Brow Long and Beattie	*J.A.M.A.*, 95 715, 1930. Cardiac Irregularities.
Davis, Robscheit-Robbins and Whipple	*J Biol. Chem.*, 133 391 1936. Liver Injury
Fabre	*C Soc. de Biol.*, 116 278, 1934 Effect on Endocrines.
Featherstone	*Anesthesiology* 8:362, 1947 Review Article.
Gold and Sussman	*Proc. Soc. Exper Biol. & Med.*, 26 3, 1928. Pupillary Reactions.
Graham	*J Exper Med* 21 185, 1915 Liver Glycogen.
Howland and Richards	*J Exper Med.*, 11 344, 1909 Liver Pathology
Middleton	*Edinburgh Lectures, Anesthesia*, 3 25 1913 Review
Nicloux and Yovanovitch	*C Soc. de Biol.*, 91 1285 1929 93 217 1929 93 272, 1929 and 93 1587 1929 Distribution in Tissues.
Pilcher and Sollman	*J Pharmacol. & Exper Therap.*, 5 340, 1915. Vasomotor Center
Sainton and Delaunay	*C Soc. de Biol.*, 122 729, 1936 Effect on Thyroid
Stewart	*Anesthesiology* 2 631, 1941 Review Article
Whipple	*J Exper Med* 15 246 1912. Liver
Whipple and Speed	*J Exper Med.*, 21 203, 1915. Liver

ETHYL CHLORIDE

Baskerville	*J Chem. and Indust. Engin.*, 5 923, 1913. Chemistry
Blalock	*Surg Gynec. & Obst.*, 46 72, 1928. Cardiac Output.
Camus and Nicloux	*C Soc de Biol.*, 115 1437 1934. Pharmacology
Embley	*Lancet*, 2:145, 1907 Circulation.
Embley	*Proc. Roy Soc. Med.*, 73:31 1906. Circulation.
Henderson and Kennedy	*Canad. M.A.J* 23 226, 1930 Pharmacology
Hewer	*Recent Advances in Anesthesia.* Clinical Use
Knoefel	*Am. J Surg* 34 494, 1936 Pharmacology
Queries and Minor Notes	*J.A.M.A.*, 138 108, 1948. Clinical Use

TRICHLORETHYLENE

Brittain	*Anesth and Analg* 27 145, 1948 Neurosurgery
Carden	*Brit. M.J* 319 1944 Trichlorethylene
Council of Pharm. & Chem.	*J.A.M.A.*, 101 1204, 1936 Pharmacology
Griffiths	*Lancet*, 242 304, 1942 Trichlorethylene
Hewer	*Proc. Roy Soc Med.*, 35 463, 1942. Trichlorethylene.
Hewer	*Recent Advances in Anesth. and Analg* 6th Ed., Philadelphia, Blakiston, 1948 Clinical Use
Jackson	*Anesth. and Analg* 13 198, 1934 Pharmacology
Krantz	*J.A.M.A.*, 108 493, 1936 Trichlorethylene
Krantz	*J Pharmacol & Exper Therap.*, 54 327 1935 Pharmacology
Waters, Orth & Gillespie	*Anesthesiology*, 4 1 1943 Cardiac Rhythm.

ALCOHOL

Adriani — *Chemistry of Anesthesia*, Springfield, Thomas, 1946. Chemistry
Beazell & Ivy — *Quart. J. Alcohol*, 1 45, 1940. Effect on Digestion.
Bruger — *Quart. J. Alcohol* 1 85, 1940. Effect on Kidney
Ellerbrook and Van Gaasbeek — *J.A.M.A.* 122 996, 1943 Alcohol.
Emerson — *Alcohol and Man*, N. Y. Macmillan Co., 1932. General Articles.
Haggard, Greenberg and Carroll — *J. Pharmacol. & Exper. Therap.* 71 349, 1941. Alcohol Diuresis.
Higgins — *J. Pharmacol. & Exper. Therap.* 9 441 1917 Respiration.
Lehman — *Proc. Soc. Exper. Biol. & Med.* 62 232, 1946 Isopropyl Alcohol.
Fries — *Arch. Surg.* 33 498, 1939 Germicide
Rosenthal — *J. Pharmacol. & Exper. Therap.*, 38 291 1930 Effect on Liver
Scheinker and Aring — *Arch. Path.* 36 615, 1943 Alcoholism.
Tennent — *Quart. J. Stud. Alcohol*, 2 263, 1941 Alcohol on Blood Sugar
Wilt — *J.A.M.A.*, 103 655, 1934 Effect on Heart.

PARALDEHYDE

Bodansky et al. — *Clinical and Experimental Data*, 6 90, 1941
Cervello — *Arch. d. Ital. di Biol.*, 6 113, 1884 First Clinical Use
Defandorf — *Am. J. M. Sc.*, 193 919, 1938 Blood Chemistry
Hitchcock and Nelson — *J. Pharmacol. & Exper. Therap.* 79 294, 1943 Paraldehyde Metabolism.
Kane and Roth — *Anesth. and Analg.* 16 121 1937 Obstetrical Use
Philip, Carmichael, et al. — *Anesthesiology*, 5 287 1944 Toxicity

TRIBROMETHANOL

Anschutz, Specht and Tiemann — *Ergebn. d. Chir. u. Orthop.* 23 406, 1930 Pharmacology
Aoki — *Tohoku J. Exper. Med.*, 25 104, 1934 Phagocytosis.
Anhelm and Tiemann — *Arch. Surg.* 29 1 1934. Pharmacology
Ashworth — *Brit. M. J.* 24 80, 1933 Purity
Bolliger and Maddox — *Anesth. and Analg.* 10 119, 1931 Pharmacology
Bourne and Raginsky — *Am. J. Surg.* 14 653, 1931 Avertin on the Liver
Bremer — *C. r. Soc. de Biol.*, 121 861 1936. Neurological Changes.
Bruger, Bourne, Dreyer — *Am. J. Surg.* 9 84, 1930 General Pharmacology
Gardner and Lamb — *J.A.M.A.*, 96 2102, 1931 Spinal Fluid Pressure
Harnack and Meyer — *Ztsch. f. Klin. Med.* 24 374 1894 Amylene Hydrate
J.A.M.A. — *Report of Council*, 109 935, 1937 Pharmacology and Chemistry
Macht — *Nature* 140 849 1937 Absorption through Skin.
Parsons — *Canad. M.A.J.* 24 50 1931 Pharmacology
Pitt — *Lancet*, 1 741, 1935. Renal Function.
Raginsky and Bourne — *Anesth. and Analg.* 11 83, 1933 Liver Function.
Schnering — *Anesth. and Analg.* 11 143, 1932 Pharmacology
Severs, Waters and Davis — *J. Pharmacol. & Exper. Therap.* 42 270, 1931 Intracranial and I tra-ocular Pressure
Veal and Brooks — *Anesth. and Analg.* 11 232, 1932. Renal Function.
Waters and Muehlberger — *Arch. Surg.* 21 887 1930. General Review
Wood — *Anesth. and Analg.* 10 187 1931. Technique
Lehman and Knoefel — *J. Pharmacol. & Exper. Therap.*, 63 453, 1938. Pharmacology
Marcotte, Clark and Livingstone — *Anesth. and Analg.* 19 86, 1940. Pharmacology
Molitor and Robinson — *Anesth. and Analg.* 17 298 1938 Pharmacology
Wood — *Anesth. and Analg.* 17 252, 1938. Clinical Article

CHLORAL HYDRATE

Adams — *J. Pharmacol. & Exper. Therap.*, 69 412, 1940. Toxicity
Alstead — *Lancet*, 1 938, 1936 Effect on Heart.
Grubfeld — *J.A.M.A.* 96 1965, 1931 Hypnotic Effect.
Lehman, Knoefel — *J. Pharmacol. Exper. Therap.* 63 453 1938 Elimination.

AMIDES, UREIDES, HYDANTOINS

Adriani — *Chem. of Anesthesia XI*. Springfield, Thomas, 1946.
Bass — *J. Pharmacol. & Exper. Therap.* 64 50 1938. Aliphatic Amides.
Burch, Hjort and DeBeer — *J. Pharmacol. & Exper. Therap.* 64 188, 1938. Amides.
Lundy and Osterberg — *Proc. Staff Meet. Mayo Clin.*, 4 386, 1929. Review

BARBITURATES

Adolph and Gerbasi	Am. J Physiol., 104 35, 1933 Blood under Amytal.
Adriani	J Lab. & Clin. Med., 25 1066, 1940. Synergisms.
Anderson, Chen, Leake	J Pharmacol. & Exper Therap 40 215, 1930. Basal Metabolism.
Argy Linegar Dille	J Pharmacol. & Exper Therap 57 258, 1936. Excretion.
Barlow	J Pharmacol. & Exper Therap., 49 268, 1936. Respiration.
Beecher and McCarroll	J Pharmacol. & Exper Therap 78:39, 1943 Barbiturates.
Beyer and Latven	J Pharmacol. & Exper Therap 181 205, 1944. Barbiturates.
Bourne, Baginsky	Surg Gynec. & Obst., 51 836, 1930 Amytal.
Burdick and Rovenstine	Ann. Int. Med., 22 819 1945. Barbiturate Poisoning.
Burstein	Proc. Soc Exper Biol. & Med., 40 122, 1939 Barbiturates.
Burstein and Rovenstine	J Pharmacol. & Exper Therap., 63 42, 1938. Parasympathetic Action.
Butturini	Boll. Soc Italia Biol., 8 836, 1933. Absorption from Stomach.
Dille	J Pharmacol. & Exper Therap 58 188, 1934 Effects on Embryo.
Dille	Am. J Obst. & Gynec., 32 318, 1936. Placental Transmission.
Duel and Chambers	J Biol. Chem., 69 214, 1946. Metabolism.
Ellis and Barlow	J Pharmacol. & Exper Therap 81 258, 1944. Pharmacology
Emge and Hoffman	Am. J Surg 9 16, 1930 Vasomotor Responses.
Evans, et al.	J Physiol., 73 67 1931 Glycogen.
Everett and Richards	J Pharmacol. & Exper Therap., 81 402, 1944. Tridione
Fiessinger and Cobb	T Am. Neurol. A., 57 441, 1931 Cerebral Circulation.
Fitch and Tatum	J Pharmacol. & Exper Therap 44 325 1932. Toxicity
Fulton and Keller	Surg. Gynec & Obst., 51 764, 1932. Dial, Amytal, Nembutal.
Gossaux, Cordill, et al.	J Lab & Clin. Med., 22 704, 1937 NPN of Urine and Blood.
Gower Tatum, et al.	J Pharmacol. & Exper Therap., 67 481, 1939 Pharmacology
Green and Koppanyi	Anesthesiology, 5 329 44. Cross Tolerance.
Gruber	Am. J Obst. & Gynec., 33 729 1937 Newer Drugs
Gruber and Baskett	J Lab & Clin. Med., 30 630, 1945. Circulation.
Gruber and Freedman	Fed. Proc., 4 121, 1945 Barbiturate Habituation.
Gruber Haury and Gruber	J Pharmacol 63 239 1938. Action on Vagi.
Gruber and Roberts	J Pharmacol., 67 349 1940 Cerebral Circulation.
Hirschfelder and Haury	Proc. Soc. Exper Biol. & Med., 30 1059 1933. Effects of Nephrectomy
Horowitz and Wessels	Proc Soc Biol & Med., 29 1016, 1934. Effects on Allergy
Horsley	Lancet, 1 141 1937 Intracranial Pressure
Irving, Berman and Nelson	Surg. Gynec. & Obst., 58 1, 1934 Obstetrical Uses.
Johnston	J Pharmacol 57 233, 1936 Action on Heart.
Keeser and Keeser	J Pharmacol. & Exper Therap., 53 137 1935. Concentration in Nervous Tissues.
Koppanyi and Dille	J Pharmacol. & Exper Therap., 52 91, 1934 Pharmacology
Koppanyi and Dille	J Pharmacol. & Exper Therap., 58 119 1936. Pharmacology
Lindemann	Am. J Psychiat 11 1063, 1932. Clinical Use
Linegar Dille Koppanyi	J Pharmacol., 58 128, 1936 Pharmacology
Lorhan	Anesthesiology 5 370, 44. Vinyl Barbital.
Masson and Beland	Fed. Proc 3 32, 1944. Barbiturate Detoxification.
Nielson, Higgins, Spruth	J Pharmacol., 26 371 1925. General Pharmacology and Excretion.
Nowak	C Soc. de Biol., 116 842, 1934. Pharmacology
Olmstead and Giragossintz	Proc Soc. Exper Biol. & Med., 27 108, 1929 Amytal.
Olmstead and Giragossintz	J Lab & Clin. Med 16 344, 1931. Amytal.
Pratt	J Pharmacol. & Exper Therap 48 234, 1933. Detoxification.
Ramsey and Haag	J Pharmacol. & Exper Therap 88:312, 1946 Barbiturates.
Ross and Weaver	Anesthesiology, 9 676, 1948. Analgesic Action.
Roth	Arch. Int. Pharmacol., 51 178, 1935. Effect on Isolated Heart.
Seeley Essex, Mann	Ann. Surg 104 332, 1936. Shock and Amytal.
Shonle	Anesth. and Analg., 11 410, 1932. Chemistry
Shonle et al.	J Am. Chem. Soc 55 853, 1936. Chemistry
Shonle Kelsch, et al.	J Pharmacol., 48 203 1933. Excretion.
Snyder	Fed. Proc., 5 97 1946 Pentobarbital in Newborn.
Swanson and Shonle	J Lab. & Clin. Med., 16 1036, 1931 Pharmacology
Tabern and Shelberg	J Am. Chem. Soc 55 328, 1933. Chemistry
Tabern and Volwiler	J Am Chem. Soc 57 1961, 1935. Thiobarbiturate Chemistry
Tod	Biochem. J 29 914, 1935. Glycemia.
Volpitto and Marangoni	J Lab. & Clin. Med., 23 575, 1938. EKG change
Wagner	J.A.M.A., 101 1787 1933. General Pharmacology

PENTOTHAL

Adams	*J.A.M.A.*, 116 681, 1941 Pentothal.
Booker	*Anesthesiology*, 7 405, 1946. Carbohydrate Metabolism.
Bourne and Pauly	*Canad. M.A.J.* 40 437 1939 Obstetrical Use
Carraway	*Anesth. and Analg.* 18 259, 1939 Clinical Use
Delmonico	*Proc. Staff Meet. Mayo Clin.*, 14 107 1939 Tests.
Draper and Whitehead	*Anesthesiology*, 5 262, 1944 Oxygenation.
Elder and Harrison	*J.A.M.A.*, 125 116, 1944. Pentothal.
Etsten and Himwich	*Anesthesiology*, 7 536, 1946. Signs and Stages.
Gruber, Haury & Gruber	*J. Pharmacol. & Exper. Therap.*, 63 193, 1938. Thiobarbiturates.
Lieberman	*J.A.M.A.* 127 1147 1945. Morphine and Pentothal.
Lundy and Mousel	*Surg. Clin. North America*, 19 1033, 1939 General Article
Mark, Fox & Burstein	*Anesthesiology*, 10 401 1949. Rectal Use
Reynolds	*Anesth. and Analg.*, 18 270 1939 Cumulative Action.

EVIPAL

Bertrand and Thiery	*C. r. Soc. de Biol.*, 119 857 1936. Lesions in Brain.
Butler	*J. Ment. Sc.* 82 131, 1936. Spinal Fluid.
Dallemagne	*J. de chir. et ann. Soc. belge de chir.* 34 274, 1935 Action on Clin.
Ernst	*Arch. Int. Pharmacod.* 48 206, 1934. Pharmacology
J.A.M.A.	*Report of the Council*, 100 1172, 1933 Pharmacology
Kennedy and Narayana	*Quart. J. Exper. Physiol.*, 24 69, 1935. Pharmacology
Storm	*Arch. Internat. de Pharmacodyn.*, 45 97 1933. Pharmacology
Tournade and Joltrain	*C. Soc. de Biol.* 119 840, 1935. Pharmacology
Tournade and Joltrain	*C. Soc. de Biol.* 121 335, 1936. Circulation.
Tournade and Joltrain	*C. Soc. de Biol.* 121 908, 1936. G.I. System

OPIUM ALKALOIDS

Berk and Sapeika	*Am. Heart J.*, 30 363, 1944 Papaverine
deBodo	*J. Pharmacol. & Exper. Therap.*, 82 74, 1944. Morphine Antidiuresis.
Eadie	*J. Biol. Chem.* 138 597 1941 Morphine
Eddy and Reid	*J. Pharmacol. & Exper. Therap.*, 52 468, 1934 Morphine and Related Alkaloids.
Elek and Katz	*J.A.M.A.*, 120 434 1942. Papaverine
Hatcher and Weiss	*Am. J. M. Sc.*, 196 742, 1938. General Article
Hamilton and Koppanyi	*Anesthesiology*, 2 437 1941 Morphine Stimulating Action.
Himmelsbach, Oberst, et al.	*J. Pharmacol. & Exper. Therap.*, 76 50, 1942. Prostigmine and Morphine
Kolb and Dumez	*Reprint No. 1443, U. S. Public Health 1931* U. S. Gov. Print. Off. Addiction.
Tatum and Seevers	*Physiol. Rev.* 11 107 1931 Addiction.
U. S. Public Health Report	*Chemistry of Opium Alkaloids*, Supplement 103, 1932

SYNTHETIC ANALGESIC DRUGS

Allen, Murphy & Meek	*Anesthesiology*, 6 149 1945 Cardiac Effects of Morphine
Batterman and Himmelsbach	*J.A.M.A.* 122 222, 1943 Demerol.
Batterman & Mulholland	*Arch. Surg.* 46 404 1943. Demerol.
Batterman and Oshlag	*Anesthesiology*, 10 214, 1949 Methadon.
Eisleb and Schaumann	*Deutsche Med. Wchnschr.* 65 967 1939
Everett	*Anesthesiology*, 9 115, 1948. Methadon.
Hardy, Wolff & Goodell	*Am. J. Physiol.*, 126 528, 1939; 129 375, 1940. Analgesics.
Lee	*J. Pharmacol. & Exper. Therap.*, 75 161, 1942. Metapon.
Lehman	*J. Lab. & Clin. Med.*, 28 787 1943 Demerol.
New and Non-official Remedies	*A.M.A.*, 1945 Papaverine
Robbins	*Anesthesiology* 10 690, 1949 Amidone.
Scott and Chen	*J. Pharmacol. & Exper. Therap.* 87 63 1946 Methadon.
Scott, Kohlstaedt & Chen	*Anes. & Analg.* 26 12, 1947 Pharmacology
Scott, Livingstone & Jacoby	*Anes. & Analg.* 26 18, 1947 Methadon
Slademan & Johnson	*J. Pharmacol. & Exper. Therap.*, 92 414, 1948. Toxicity
Tallow and Bauer	*New England J. Med.*, 233 134, 1945 Cobra Venom.
Way	*J. Am. Pharm. A. Sc. Ed.*, 35 44, 1946. Isonipecaine

LOCAL ANESTHETICS

Adriani	
Barbour and Tovell	*South. M. J.* Chemistry and Pharmacology
	Anesthesiology, 9 514 1948, Intravenous Procaine

BARBITURATES

Adolph and Gerbasi — *Am. J Physiol., 106*:85, 1933. Blood under Amytal.
Adriani — *J Lab. & Clin. Med 24* 1066, 1940. Synergisms.
Anderson, Chen, Leake — *J Pharmacol. & Exper Therap., 40*:215, 1930 Basal Metabolism.
Argy Linegar Dille — *J Pharmacol. & Exper Therap., 57* 295, 1936. Excretion.
Barlow — *J Pharmacol. & Exper Therap 49* 208, 1936 Respiration.
Beecher and McCarroll — *J Pharmacol. & Exper Therap., 78*:30 1943. Barbiturates.
Beyer and Latven — *J Pharmacol. & Exper Therap., 181* 203, 1944 Barbiturates.
Bourne, Baginsky — *Surg., Gynec. & Obst., 51*:856, 1930 Amytal.
Burdick and Rovenstine — *Ann. Int. Med., 22*:819, 1945 Barbiturate Poisoning.
Burstein — *Proc. Soc. Exper Biol. & Med., 40* 122, 1939 Barbiturates.
Burstein and Rovenstine — *J Pharmacol. & Exper Therap 63* 42, 1938. Parasympathetic Action.
Butturini — *Boll. Soc. Italia Biol., 8* 296, 1933 Absorption from Stomach.
Dille — *J Pharmacol. & Exper Therap., 52*:129 1934 Effects on Embryo.
Dille — *Am. J Obst. & Gynec., 32*:328, 1936. Placental Transmission.
Deuel and Chambers — *J Biol. Chem., 69* 214, 1926. Metabolism.
Ellis and Barlow — *J Pharmacol. & Exper Therap., 24* 296, 1924 Pharmacology
Engle and Hoffman — *Am. J Surg 9* 16, 1930. Vasomotor Responses.
Evans, et al. — *J Physiol 72*:67 1931. Glycogen.
Everett and Richards — *J Pharmacol. & Exper Therap 81* 402, 1944. Tridione
Finesinger and Cobb — *Tr Am. Neurol. A 57* 441, 1931 Cerebral Circulation.
Fitch and T tum — *J Pharmacol. & Exper Therap 44* 325 1932. Toxicity
Fulton and Keller — *Surg Gynec & Obst., 54* 764, 1932. Dial, Amytal, Nembutal.
Gessaux, Cordill, et al. — *J Lab. & Clin. Med., 22*:704, 1937 NPN of Urine and Blood.
Gower Tatum, et al. — *J Pharmacol. & Exper Therap., 37* 481 1930. Pharmacology
Green and Koppanyi — *Anesthesiology 5*:329, 44 Cross Tolerance.
Gruber — *Am. J Obst. & Gynec., 33* 729, 1937 Newer Drugs.
Gruber and Baskett — *J Lab. & Clin. Med., 10* 630, 1925 Circulation.
Gruber and Freedman — *Fed. Proc., 4* 121 1945 Barbiturate Habituation.
Gruber Haury and Gruber — *J Pharmacol., 63* 230 1938. Action on Vagi.
Gruber and Roberts — *J Pharmacol., 27* 349 1926. Cerebral Circulation
Hirschfelder and Haury — *Proc. Soc. Exper Biol. & Med., 30*:1059, 1933. Effects of Nephrectomy
Horowitz and Wessels — *Proc. Soc. Biol. & Med., 29*:1016, 1932. Effects on Allergy
Horsley — *Lancet, 1* 141 1937 Intracranial Pressure.
Irving, Berman and Nelson — *Surg Gynec. & Obst 58* 1, 1934. Obstetrical Uses.
Johnston — *J Pharmacol., 57*:333, 1936. Action on Heart.
Keeser and Keeser — *J Pharmacol. & Exper Therap., 63* 137 1935. Concentration in Nervous Tissues.
Koppanyi and Dille — *J Pharmacol. & Exper Therap., 52*:91 1934. Pharmacology
Koppanyi and Dille — *J Pharmacol. & Exper Therap 63* 119 1936. Pharmacology
Lindemann — *Am. J Psychiat., 11* 1083, 1932. Clinical Use
Linegar Dille, Koppanyi — *J Pharmacol., 58* 128, 1936. Pharmacology
Lorhan — *Anesthesiology, 5* 370, 44. Vinyl Barbital.
Masson and Beland — *Fed. Proc., 3* 32, 1944 Barbiturate Detoxification.
Nielson, Higgins, Spruth — *J Pharmacol., 26* 371 1925. General Pharmacology and Excretion.
Nowak — *C Soc. de Biol., 116* 642, 1934. Pharmacology
Olmstead and Giragossintz — *Proc. Soc. Exper Biol. & Med., 27* 103, 1929 Amytal.
Olmstead and Giragossintz — *J Lab. & Clin. Med 16* 384 1931. Amytal.
Pratt — *J Pharmacol & Exper Therap., 48* 285, 1933 Detoxification.
Ramsey and Haag — *J Pharmacol. & Exper Therap., 88* 313, 1946. Barbiturates.
Ross and Weaver — *Anesthesiology, 9* 270, 1948 Analgesic Action.
Roth — *Arch. Int. Pharmacod., 51* 170, 1935 Effect on Isolated Heart.
Seeley Essex, Mann — *Ann. Surg., 104* 332, 1936. Shock and Amytal.
Shonle — *Anesth. and Analg 11* 210, 1932. Chemistry
Shonle et al. — *J Am. Chem. Soc 58*:585, 1936. Chemistry
Shonle Kritch, et al — *J Pharmacol., 49*:393, 1933. Excretion.
Snyder — *Fed. Proc., 5*:97 1946 Pentobarbital in Newborn.
Swanson and Shonle — *J Lab. & Clin. Med., 16* 1056, 1931 Pharmacology
Tabern and Shelberg — *J Am. Chem. Soc., 55*:328, 1933 Chemistry
Tabern and Volwiler — *J Am. Chem. Soc., 57* 1961, 1935. Thiobarbiturate Chemistry
Ted — *Biochem. J 29* 914, 1934. Glycemia.
Volpitto and Marangoni — *J Lab. & Clin. Med., 23*:575, 1938. EKG change
Wagner — *J A.M.A., 101* 1787 1933 General Pharmacology

PENTOTHAL

Adams — *J.A.M.A.*, 126:232, 1944. Pentothal.
Booker — *Anesthesiology*, 7:405, 1946. Carbohydrate Metabolism.
Bourne and Pauly — *Canad. M.A.J.*, 40:437, 1939. Obstetrical Use.
Carraway — *Anesth. and Analg.*, 18:258, 1939. Clinical Use.
Delmonico — *Proc. Staff Meet. Mayo Clin.*, 14:100, 1939. Tests.
Draper and Whitehead — *Anesthesiology*, 5:262, 1944. Oxygenation.
Elder and Harrison — *J.A.M.A.*, 125:116, 1944. Pentothal.
Etsten and Himwich — *Anesthesiology*, 7:536, 1946. Signs and Stages.
Gruber, Henry & Gruber — *J. Pharmacol. & Exper. Therap.*, 63:193, 1938. Thiobarbiturates.
Lieberman — *J.A.M.A.*, 127:1147, 1945. Morphine and Pentothal.
Lundy and Mousel — *Surg. Clin. North America*, 19:1033, 1939. General Article.
Mark, Fox & Burstein — *Anesthesiology*, 10:401, 1949. Rectal Use.
Reynolds — *Anesth. and Analg.*, 18:270, 1939. Cumulative Action.

EVIPAL

Bertrand and Thiery — *C. r. Soc. de Biol.*, 118:837, 1934. Lesions in Brain.
Butler — *J. Ment. Sc.*, 83:131, 1934. Spinal Fluid.
Dallemagne — *J. de chir. et ann. Soc. belge de chir.*, 34:298, 1935. Action on Cilia.
Ernst — *Arch. Int. Pharmacol.*, 63:298, 1936. Pharmacology.
J.A.M.A. — *Report of the Council*, 105:1172, 1935. Pharmacology.
Kennedy and Narayana — *Quart. J. Exper. Physiol.*, 24:90, 1935. Pharmacology.
Storm — *Arch. Internat. de Pharmacodyn.*, 48:97, 1933. Pharmacology.
Tournade and Joltrain — *C. r. Soc. de Biol.*, 119:240, 1935. Pharmacology.
Tournade and Joltrain — *C. r. Soc. de Biol.*, 121:383, 1935. Circulation.
Tournade and Joltrain — *C. r. Soc. de Biol.*, 121:908, 1936. G.I. System.

OPIUM ALKALOIDS

Berk and Saperka — *Am. Heart J.*, 30:248, 1945. Papaverine.
deBodo — *J. Pharmacol. & Exper. Therap.*, 82:74, 1944. Morphine Antidiuresis.
Eadie — *J. Biol. Chem.*, 138:597, 1941. Morphine.
Eddy and Reid — *J. Pharmacol. & Exper. Therap.*, 52:468, 1935. Morphine and Related Alkaloids.
Elek and Katz — *J.A.M.A.*, 120:434, 1942. Papaverine.
Hatcher and Weiss — *Am. J. M. Sc.*, 196:743, 1938. General Article.
Hazelton and Koppanyi — *Anesthesiology*, 2:427, 1941. Morphine, Stimulating Action.
Himmelsbach, Oberst, et al. — *J. Pharmacol. & Exper. Therap.*, 76:50, 1942. Prostigmine and Morphine.
Kolb and Dumez — *Reprint No. 1463, U. S. Public Health 1931*. U. S. Gov. Print. Off. Addiction.
Tatum and Seevers — *Physiol. Rev.*, 11:107, 1931. Addiction.
U. S. Public Health Report — *Chemistry of Opium Alkaloids*, Supplement 103, 1932.

SYNTHETIC ANALGESIC DRUGS

Allen, Murphy & Mark — *Anesthesiology*, 6:140, 1945. Cardiac Effects of Morphine.
Batterman and Himmelsbach — *J.A.M.A.*, 122:222, 1943. Demerol.
Batterman & Mulholland — *Arch. Surg.*, 46:404, 1943. Demerol.
Batterman and Oshlag — *Anesthesiology*, 10:214, 1949. Methadon.
Elsleb and Schaumann — *Deutsche Med. Wchnschr.*, 65:967, 1939.
Everett — *Anesthesiology*, 9:115, 1948. Methadon.
Hardy, Wolff & Goodell — *Am. J. Physiol.*, 126:523, 1939; 129:578, 1940. Analgesics.
Lee — *J. Pharmacol. & Exper. Therap.*, 75:161, 1942. Metapon.
Lehman — *J. Lab. & Clin. Med.*, 28:787, 1943. Demerol.
New and Non-official Remedies — *A.M.A.*, 1943. Papaverine.
Robbins — *Anesthesiology*, 10:290, 1949. Amidones.
Scott and Chen — *J. Pharmacol. & Exper. Therap.*, 88:90, 1944. Methadon.
Scott, Kohlstaedt & Chen — *Anes. & Analg.*, 26:12, 1947. Pharmacology.
Scott, Livingstone & Jacoby — *Anes. & Analg.*, 26:18, 1947. Methadon.
Shideman & Johnson — *J. Pharmacol. & Exper. Therap.*, 92:414, 1948. Toxicity.
Talker and Bauer — *New England J. Med.*, 229:152, 1943. Cobra Venom.
Way — *J. Am. Pharm. A., Sc. Ed.*, 35:44, 1946. Isonipecaine.

LOCAL ANESTHETICS

Adriani — *South. M. J.* Chemistry and Pharmacology.
Barbour and Tovel — *Anesthesiology*, 9:514, 1948. Intravenous Procaine.

Bieter	*Am. J. Surg.* 34:500, 1936. Pharmacology of Local Anesthetics.
Bieter and Hirschfelder	*Physiol. Rev.*, 14 190, 1934. Local Anesthetics.
Bigelow and Harrison	*J. Pharmacol. & Exper. Therap.* 81 368, 1944. Procaine
Boothe	*Ill. Dental J.* 10:343 1941 Local Anesthetics.
Bremer and Titeca	*C. r. Soc. de Biol.*, 103 873, 1930. Novocaine.
Coles and Rose	*J. Lab. & Clin. Med.*, 15 390, 1930 Action on Cornea.
Dunlop	*Proc. Staff Meet. Mayo Clin.*, 9 241, 1934. Fate of Procaine.
Eggleston and Hatcher	*J. Pharmacol. & Exper. Therap.*, 13 433, 1919 Pharmacology
Gasser and Erlanger	*Am. J. Physiol.*, 88:581 1929. Effect of Size of Fiber
Gilman, Goodman, et al.	*J. Pharmacol. & Exper. Therap.*, 74 290, 1942. Local Anesthetics.
Graubard and Peterson	*Pharmacology.* Springfield, Thomas, 1950. Intravenous Procaine.
Hamel and Lamont	*Anesthesiology*, 8 596, 1947 Bromsalizol.
Hill and MacDonald	*J. Pharmacol. & Exper. Therap.*, 53:454, 1935 Respiration.
Hingson	*J.A.M.A.*, 126 1129 1944 Caudal Analgesia.
Mayer	*J.A.M.A.*, 82 876, 1924. Toxicity
Potter and Whitacre	*Anesthesiology*, 7 400, 1946 Potentiation by Ephedrine
Richards and Kueter	*J. Pharmacol. & Exper. Therap.*, 87 42, 1946. Procaine
Wartl	*Anesthesiology*, 2 74, 41 Detoxification.

SPINAL ANESTHESIA

Babcock	*Anesth. and Analg.* 4 222, 1925 Blood Pressure
Bagley	*Arch. Surg.* 1 16, 30 1928. Blood in Spinal Fluid.
Baldes, Herrick & Essex	*Proc. Staff Meet. Mayo Clin.*, 7 653, 1932. Lumbar Sympathectomy
Bradshaw	*Ann. Surg.* 104 41, 1936 Circulation.
Bower, Clark, Wagoner & Burns	*Surg. Gynec. & Obst.* 64 636, 1932. Circulation.
Brock, Bell and Davidson	*J.A.M.A.*, 109 441 1936. Nervous Complications.
Burch and Harrison	*Arch. Surg.*, 21:330, 1930. Cardiac Output.
Burch, Harrison & Blalock	*Arch. Surg.*, 21 693 1930 Effects of Hemorrhage
CoTui	*Arch. Surg.* 33 825, 1936. General Physiology
Davis	*South. M.J.* Physiology 40:390, 1947
Davis, et al.	*J.A.M.A.*, 97 1781, 1931. Pathology
Dood and Rovenstine	*Anesthesiology*, 1 64, 1940 Circulation Time.
Elliott	*J. Physiology*, 44:374, 1912. Suprarenal Glands.
Emmett	*J.A.M.A.* 102 425 1934. Effect of Procaine
Ferguson and North	*Surg. Gynec. & Obst.* 54 621 1932 General Observations
Gask and Ross	*The Surgery of the Sympathetic Nervous System*, New York, W. Wood and Co., 1934.
Gray and Parsons	*Quart. J. Med.*, 5 339 1912 Circulation.
Harrison and Frank	*Arch. Surg.* 26:571 1932 Respiratory Paralysis.
Heymans, Bouckaert and Bert	*C. r. Soc. de Biol.* 118:718, 1933 Carotid Sinus.
Heymans, Bouckaert, Farber and Hsu	*Am. J. Physiol.* 117 619 1936. Vasomotor Reflexes.
Hill and MacDonald	*J. Pharmacol. & Exper. Therap.* 47 161, 1933. General Observations.
Isaac, et al.	*Surg. Gynec. & Obst.* 51:76, 1930. Changes in Spinal Fluid.
Koster, Shapiro, et al.	*Am. J. Surg.* 36 248, 1934. Procaine Concentration.
Koster and Kasman	*Am. J. Surg.* 80 277 1934 Pathological changes.
Labat	*Nelson's Loose Leaf Surgery*, New York, Thomas Nelson & Sons, 1931 Regional Anesthesia.
Latterel and Lundy	*Anesthesiology*, 10:657 1949 Blood Gases.
Maxson	*Spinal Anesthesia*, New York, J. B. Lippincott Co. 1938
Rabeltra, Hamrich and DuBois	*J. Pharmacol. & Exper. Therap.* 52 437 1934. Morphine
Schuberth	*Acta chir. Scandinav.*, 78 sup. 48, 1, 1936. Circulation.
Seevers and Waters	*California and West. Med.*, 35 169 1931 Circulation.
Shaw, Steele and Lamb	*Arch. Surg.* 35:803, 1937 Blood Oxygen.
Smith, Goldring and Chasis	*J. Clin. Investigation*, 17 263, 1938. Kidney Physiology
Smith, Rovenstine, et al.	*J. Clin. Investigation*, 18:319 1939 Circulatory Studies
Smith and Porter	*Am. J. Physiol.*, 38 108, 1915. Experimental Studies
Steinberg and Bishop	*Anesthesiology* 7 690, 1946. Nerve Palsies

CURARE AND CURARE-LIKE COMPOUNDS

Cole	*Anesthesiology* 7 190, 1946. Lethal Doses of Curare.
Comroe and Dripps	*Anesthesiology* 7:260, 1946 Histamine-like Action
Cullen and Gross	*Anesthesiology* 6 231, 1945 Effect on Smooth Muscle
Dripps and Sergent	*Anesthesiology* 8 241, 1947 Erythroidine.
Gill	*Anesthesiology*, 14, 1946 Discovery and Development.

Griffith, Bourne et al.	*Anesthesiology*, 10:61 1949 Myanesin.
Griffith and Johnson	*Anesthesiology*, 3 418, 1942. Clinical Use
Harbord, Beckert and Hathaway	*Anesthesiology*, 7 24 1946. Curare-Nitrous Oxide
Hewer et al.	*Anesthesiology*, 14 817 1949 Syncurine
Organe, Paton, Zaimis	*Lancet*, 1 21, 1949. Syncurine
Robbins and Lundy	*Anesthesiology* 8 252, 1947; 8 348, 1947 Review
Schallek	*Proc Soc. Exper Biol. & Med.*, 63 79 1946 Ether and Curare
Smith, Lutterel & Fleckman	*Science* 110:94, 1949 Curare-like Compounds.
Swanson, Henderson & Chen	*J Lab & Clin. Med.*, 24 518, 1949 Metubine
Whitacre and Fisher	*Anesthesiology*, 6 124 1945 Clinical Use
Wyngaarden, Triebe and Seevers	*Anesthesiology*, 10:517 1949 Myanesin.

ANALEPTIC DRUGS

Anderson	*Ann. Int. Med* 14 2037 1941 Picrotoxin and Barbital.
Barlow	*J Pharmacol. & Exper Therap.*, 55 1 1935 General Article.
Barlow	*J Lab. & Clin. Med.*, 23 601, 1938. General Pharmacology
Brazier Miles and Finesinger	*Anesthesiology*, 10:23, 1949 Sodium Succinate
Burn	*Brit. M.J* 1 989 1939 General Pharmacology
Burstein and Rovenstine	*Anesth. and Analg* 16 151, 1937 Clinical Use
Chen	*Brit M.J* 2 993, 1947 Analeptics.
Dille	*J Pharmacol.*, 64 310, 1938. Elimination of Picrotoxin.
Draper and Whitehead	*J Pharmacol. & Exper Therap.*, 66 10, 1939 Metrazol.
Dripps, Kirby and Johnson	*Ann. Surg* 127:952, 1948 Cardiac Resuscitation.
Eckinhoff, Schmidt, et al.	*J.A.M.A* 139 780, 1949. Present Status on all Drugs.
Eggleston	*J.A.M.A* 107 1212, 1936 General Article.
Levy and Krumbhaar	*Am. J Med Sc.*, 193 785, 1939 Benzedrine
Fournier and Selye	*Fed. Proc.*, 1 25, 1942. Metrazol.
Henderson and Sparks	*Univ. Toronto Med. J* April, 1947 Respiratory stimulants.
Hildebrandt	*Gunners, Handbuch der Exper Pharmacol.*, 5 151 1938. Metrazol.
Jackson	*J Lab. & Clin. Med.*, 20 1 118, 1934. Reactions on Nervous System.
Klein	*J Biol. Chem.*, 151 641, 1943. Picrotoxin.
Kopanyi, Linegar and Dille	*J Pharmacol. & Exper Therap* 58 199 1936. Picrotoxin.
Larkan	*Anesth. and Analg* 17 44, 1938. Neosynephrin.
Marshall, et al.	*J Pharmacol. & Exper Therap.*, 60 472, 1937 Picrotoxin.
Pruschmadt, Ramseyd and Haag	*J Pharmacol. & Exper Therap.*, 83 45, 1945 Barbiturate and Succinate
Raginsky	*T Internat. Coll. Surg* 1 66, 1938. General Article
Rosenthal	*J Pharmacol. & Exper Therap* 71 305, 1941; Ibid 73 448, 1941 Picrotoxin.
Ross	*J.A.M.A* 123 443, 1943 Artificial Respiration.
Tatum and Kozelka	*J Pharmacol. & Exper Therap* 72 284 1941 Metrazol.
Tatum and Werner	*J Pharmacol & Exper Therap.*, 60 240, 1939 Picrotoxin, Metrazol, Coramine.
Touhy and Essex	*Surgery*, 1 341, 1937 Cobefrin.
Wood	*Anesth and Analg* 14 1, 1935 General Clinical Article
Wood	*Am J Surg* 22 98, 1933 General Clinical Article

SYMPATHOMIMETIC DRUGS

Anderson	*Anesthesiology*, 7 1, 1940. Methedrine
Bray Katz and Adriani	*Anesthesiology* 10 40, 1949 Vasoconstrictors for Spinal Anesthesia
Henderson	*Anesthesiology*, 1 322, 1940. Review Article
Jang	*J Pharmacol & Exper Therap.*, 71 87 1941 Sympatholytic Agents.
Melville	*Anesthesiology*, 7 1940, 1946. Ephedrine and Pituitrin.
Morton and Tainter	*J Physiol.*, 98 263, 1940. Sympathomimetic Amines.
Nicholson & Werle	*Lahey Clin. Bull.*, 7 204, 1948. Review
Romero and Adriani	*South. M.J* 38 243, 1945 Ornethyl.
Scott and Chen	*Fed Proc* 5 201, 1946. Morphine Substitutes.
Viets	*Am J.M Sc* 208:701 1944. Neostigmine.
Yonkel and Selden	*Anesthesiology*, 9 605, 1948. Desoxyephedrine

INORGANIC GASES

Adriani	*Chemistry of Anesthesia*, Springfield, Thomas, 1946. Chemistry
Adriani and Batten	*Anesthesiology*, 3 401 1942. Chemistry
Armstrong	*Military Surgeon*, Aug. 1939. Oxygen Poisoning.

Barach	*Ann. Int. Med.*, 9 739 1935. Helium.
Behnke	*Anesth. and Analg* 19:35, 1940. Rare Gases.
Behnke and Yarbrough	*U S Naval Med. Bull.*, 36:542, 1938. Helium.
Bonham	*Anesth. and Analg* 18:54, 1939 Helium.
Burford	*Anesth. and Analg* 17 241 1938. Inert Gases.
Coryllos and Birnbaum	*Am J.M Sc* 183 317 1932. Pulmonary Absorption.
Eastman, Dunn and Kreiselman	*Am. J Obst. & Gynec* 36:571, 1938. Oxygen and CO_2.
Eversole	*Anesth. and Analg.*, 17 241, 1938. Helium.
Heil	*This Physical World*. Philadelphia, Blakiston, 1936. Physics.
Wang and Winn	*J Pharmacol. & Exper Therap.*, 92 187 1948. Carbon Dioxide

ANOXIA

Alexander and Himwich	*Am. J Physiol.*, 126 418, 1939 Acute Anoxia in Man.
Barach and Rovenstine	*Anesthesiology* 6 449, 1945. Nitrous Oxide and Anoxia.
Baxter White et al.	*Naval Med. Bull.*, 42 1103, 1944 Anoxia.
Burdick and Lisa	*Anesthesiology* 10:303, 1949 Central Effects.
Chase	*Surg Gynec. & Obst.*, 73 105, 1941 Effect during Surgery
Courville	*Anesthesiology* 2 44, 1941 Anoxia and Ether
Echols, O'Neal and Sloan	*Anesthesiology* 10 164, 1949 With Nitrous Oxide
Emerson and Van Liere	*J Lab. & Clin. Med.*, 28:689, 1943. Anoxia.
Himwich	*Anesthesiology*, 10 663 1949. Symptomatology

CARBON DIOXIDE ABSORPTION

Adriani and Batten	*Anesthesiology* 3:1, 1942. Baralyme
Adriani and Rovenstine	*Anesthesiology*, 2:1 1941. CO_2 Absorption.
Brown	*U S Naval Med. Bull.*, 28 523, 1930. Hypercapnia in Normal Subjects.
Goldstein and Dubois	*Am. J Physiol.*, 81 650, 1927 Circulatory Effects.
Leake and Waters	*Anesth and Analg* 8 17 1929 Hypercapnia.
Rovenstine	*Am. J Surg* 22:400, 1933. Absorption.
Seevers, Stormont, Hathaway and Waters	*J.A.M.A* 15:2131, 1940. Acapnia.
Waters	*Canad. M.A.J* 38 240, 1938. Toxicity
Waters	*New Orleans M and S.J* 90:219, 1937 Toxicity under Narcosis.
Waters	*Proc. Roy Soc. Med.*, 30:11, 1932. Absorption.

EXPLOSIONS

Bachman and Wardell	*Ohio Chem. Co. Bull.*, 178:1930. Explosion.
Cooper	*T Am. Soc. Anesth.*, 5 2, 1939 Explosion.
Woodbridge Horton and Connell	*J.A.M A.*, 113:740, 1939 Intercoupling

PREMEDICATION

Anderson	*Proc. Soc. Exper Biol. & Med.*, 27 102, 1929 Morphine
Carlson	*Anesth. and Analg* 13:221 1934 Intestinal Activity
Chassin and Lusk	*J Pharmacol. & Exper Therap.*, 19:259, 1922. Heat Production.
Conroe	*J.A M.A.*, 101 446, 1933. *J.A.M.A.*, 128 848, 1945. Atropine.
Henderson	*Anesthesiology*, 9 73, 1949 Premedication in Obstetrics.
Leigh and Belton	*Anesthesiology* 7 611 1946. Premedication in Children.
Phelps	*Anesthesiology*, 3:71 1942. Belladonna Alkaloids
Wangeman and Hawk	*Anesthesiology*, 3:11 1942. Morphine and Scopolamine.
Waters	*Texas State J Med.*, 31:304, 1935. Morphine, Scopolamine and Atropine.

PROCEDURES

Adriani	*Techniques and Procedures of Anesthesia*. Springfield, Thomas, 1948.
Alexander and Cullen	*Am J Surg* 31 425, 1936 Premedication.
Blennard	*Canad M.A.J* 58 186, 1948. Thoracic Surgery
Dunlop	*Anesth and Analg* 18:201, 1939 Thoracic Surgery
Gwathmey and Hoge	*Anesth. and Analg* 18:249 1939 Rectal Anesthesia.
Knight	*Minnesota Med. J* 22:2, 1939. General Article
Leigh and Belton	*Pediatric Anesthesia* N Y MacMillan, 1949 General Article
Lundy	*Clinical Anesthesia*. Saunders, 1943
Magill	*Anesth and Analg* 9 161 1931 Intratracheal Anesthesia
Magill	*Am J Surg* 34 450, 1936 Intratracheal Anesthesia.

Rovenstine	*Surg. Gynec. & Obst.*, 63:325, 1936. Thoracic Surgery
Shields	*Anesth. and Analg.* 17 211 1938. General Procedures.
Tuohy	*Proc. Staff Meet. Mayo Clin.*, 13:457 1938. General Article

REFLEXES

Allen	*Am. J. Physiol.*, 115:579 1936. Respiratory Reflexes with Anesthesia.
Brewer, Luckhardt, et al.	*Anesth. and Analg.* 13 257 1934 Reflex of Glottis with Stimulation of Viscera.
Draper and Whitehead	*Anesthesiology*, 8 189 1947 Reflex from Chest Wall.
Heymans	*New England J. M.* 219 157 1938. Carotid Sinus.
Hill	*Quart. J. Exper. Physiol.* 23 79 1932. Effect of Anesthesia on Carotid Sinus.
Reid and Brace	*Anesthesiology*, 4:345, 1943 Respiratory Reflexes.
Rovenstine and Cullen	*Surg.* 6 167 1939 Carotid Sinus.
Schmidt	*Am. J. Physiol.*, 102:119 1932. Carotid Sinus.
Vercauteren	*Arch. Int. de Pharmacol. et de Therap.* 43 399 1932. Effects of Anesthesia on Carotid Sinus.

COMPLICATIONS

Adriani	*Techniques and Procedures of Anesthesia.* Springfield, Thomas, 1946.
Bookhammer and Cullen	*Anesthesiology*, 4 265, 1943 Pulmonary Edema.
Brace	*Anesthesiology*, 3 131 1942. Atelectasis.
Burford	*Anesthesiology* 1:208, 1940 Hyperthermia.
Burstein and Rovenstine	*Anesth. and Analg.* 17 134, 1938. Coeliac Plexus Reflex.
Cassels and Gittelson	*Anesthesiology* 9 46, 1948. Diaphragmatic Paralysis.
Clement	*Anesth. and Analg.* 16 271, 1937 Shock.
Cullen and Rovenstine	*Anesth. and Analg.*, 17 13, 1938. Thoracic Surgery
Dodd and Rovenstine	*Anesthesiology* 7 291 1946 Fat Embolism.
Drew	*Anesthesiology*, 3 178 1946 Shock.
Elman and Brown	*War Med.*, 5:477 1943. Shock.
Eversole	*Anesthesiology*, 1 72, 1940. Pulmonary Complications.
Lahey and Hoover	*Ann. Surg.* 108:545, 1938. Laryngeal Nerve Palsies.
Petersen and Paffin	*Anesthesiology*, 3 70, 1942. Atelectasis.
Peterson and Rovenstine	*Anesth. and Analg.* 15 300, 1936. Tracheal Collapse
Reid and Brace	*Surg. Gynec. & Obst.*, 70:157 1940. Respiratory Reflexes.
Rearnow and Tovell	*Am. J. Surg.* 34 468, 1936 Convulsions.
Rovenstine	*Anesth. and Analg.* 14 40, 1935. Convulsions.
Rovenstine and Taylor	*Am. J. M. Sc.*, 191 807 1936 Pulmonary Complications.
Smith	*Lancet*, 246 52, 1944. Anesthesia Convulsions.
Symmers	*Am. J. Surg.* 26 7 1934 Status Lymphaticus.
Taylor, Bennett and Waters	*Anesth. and Analg.* 16 187 1937 Pulmonary Complications.
Waters	*Anesthesiology*, 1 316, 1940 Bronchopneumonia.
Wilcox and Tovell	*Anesth. and Analg.* 18 94, 1939 Diabetes.
Wolman	*Wisconsin M. J.* 35 457 1936. Neurological Complications
Wood and Jacoby	*J. Pharmacol. & Exper. Therap.* 79 250 1943. Hemorrhage in Anesthesia.

REFERENCES TO FOURTH EDITION

GENERAL REFERENCES

Adriani	*Anesth. & Analg* 37:1, 1958. Uncommon Diseases and Anesthesia.
Adriani and Parmley	*The Recovery Room*, Springfield, Thomas, 1958.
Barlow	*Chemical Pharmacology*, New York, John Wiley 1955.
Burstein	*Anesth. & Analg* 26:32, 1947 Reflexes.
Dripps, Vandam and Eckenhoff	*Introduction to Anesthesia*, Philadelphia, Saunders, 1958.
Lott	*Anesth. & Analg* 33 461, 1900. Medicinal Chemistry
Marsh	*Fundamental Pharmacology* Springfield, Thomas, 1951.
Nash	*Surgical Physiology*, Springfield Thomas, 1953.
Pittinger	*Anesth. & Analg.*, 36:36, 1957 New Drugs.
Quilligan, Hedbrink and Hingson	*Anesth. & Analg.*, 36 33, 1957 Cardiac Output.
Schesler	*Anesth. & Analg* 37:306, 1958. Cholinergic Function.
Swartz, Papper and Ngai	*Manual of Anesthesiology*, Springfield, Thomas, 1957
Swerdlow	*Anesth. & Analg* 33 292, 1900. Parasympathetic Drugs.
Waters	*Chloroform*, Madison, Univ Wisconsin Press, 1951.

THEORIES OF NARCOSIS

Butler	*Pharm. Rev.*, 2:121, 1950. Review
Gerard	*Anesthesiology* 8:453, 1947 Review
Mullins	*Chem. Rev.*, 54 289, 1954 Review
Wulf and Featherstone	*Anesthesiology*, 18 97 1957 Van der Waal's Constants.

HYDROCARBONS

Krantz, et al.	*Anesthesiology*, 10:623, 1949. Cyclobutane.
Price, Conner and Dripps	*Anesthesiology*, 14 1-8, 1953. Cyclopropane.
Robbins	*Cyclopropane anesthesia*, Baltimore, Wilkins, 1958.
Virtue	*Anesthesiology* 10:318, 1949 Cyclopentane.
Summers	*Anesth. & Analg* 39 13, 1900. Spiropentane.

ETHER

Artusio and Ebersole	*Anesthesiology*, 19:607 1958. Analgesia.
Brewster Isaacs, Wain and Anderson	*Am. J Physiol.*, 175:399 1953. Cardio-adrenal Response.
Harmel, Ikezono, et al.	*Anesthesiology*, 20 507 1959 Ventilation.
Neely and Skokys	*Anesthesiology*, 19 671, 1958. Peroxides.
Papper et al.	*J.A.M.A.*, 151:1690, 1953. Renal Function.
Price, et al.	*Anesthesiology* 20 563, 1959. Sympatho-Adrenal Responses.

ETHYL VINYL ETHER (VINAMAR)

Dornette and Orth	*Anesth. & Analg* 1 240, 1950. Pharmacology
Krantz	*J Pharmacol. & Exper Therap.*, 89 86, 1947 Pharmacology
Sadove, Wyant and Gletcher	*Anesth. & Analg* p435-440, July 1953. Pharmacology

TRI FLUORO ETHYL VINYL ETHER (FLUOROMAR)

Krantz	*J Pharmacol. & Exper Therap.*, 108 488, 1953. Pharmacology
Krantz, et al.	*Anesthesiology* 10:1, 1941. Pharmacology

HALOGENATED HYDROCARBONS

Bush, Bittenbender and Adriani	*Anesthesiology*, 13:197 1952. Ethyl Chloride.
Cohen and Cohen	*Anesthesiology*, 19 79-108, 1958 Trichlorethylene.
Stephen and Hall	*Anesthesiology*, 14 33, 1953 Trichlorethylene.
Atkinson	*Anesthesiology*, 21:167 1960. Trichlorethylene.

FLUOTHANE

Johnstone	*Brit. J Anesth.*, 28:392, 1956. Cardiovascular Effects.
Johnstone, Bernan and Hunter	*Lancet*, 2 433, 1957 Pharmacology
New and Non-Official Drugs	A.M.A. Chicago, 1960. Gen Pharmacology
Raventos	*Brit. J Pharmacol* 11 394, 1956. Gen Pharmacology
Robbins	*J Pharmacol. & Exper Therap* 85 197 1946. Structure and Activity
Severinghaus and Cullen	*Anesthesiology*, 19:770, 1958. Cardiac Effects.
Stephen, Margolis and Fabian	*Anesthesiology* 19 770, 1958. Gen. Pharmacology
Vandam, Burnap and Gallo	*Anesthesiology*, 19:287 1955. Circulatory Effects.

NARCOTICS

Annals	*New York Acad. Sc.*, 51 1 174, 1948. Newer Synthetic Analgesics.
Brotman, Cullen and Wilkins	*Anesthesiology*, 11 587 1950. Dromoran.
Eckenhoff	*Anesthesiology* 20:858-858, 1959. Phenazocine.
Foldes and Kentman	*New England M* 244 296-298, 1951 Dromoran.
Hepke and Barnes	*Am. J Obst. & Gynec.*, 58:800-801, 1949 Nisentil.
Merck Index	Vol. III Merck and Co., Rahway N J 1960. Chemistry of Individual Drugs.
New and Non-Official Drugs	A.M.A., Chicago, 1960. Individual Drugs.
Orahovats, Lehman and Chaplin	*J Pharmacol. & Exper Therap.*, 119 90, 1957 Anileridine.
Reynolds and Randall	*Morphine and Allied Drugs*, Toronto, Univ Toronto Press, 1957
Wikler	*Public Health Monograph #52*, Publication 589. U S. Pub. Health Service, 1958.

TRANQUILIZERS AND NON BARBITURATE HYPNOTICS

Ayd	*J Med. Soc. of N Y.*, 57 4, 1960. Current Status.
Ayd	*Current Therap. Research*, 1 41, 1959. Clinical Use
Barth and Adriani	*J Sou. Med. Assoc* 49 1274, 1956. Viadril.
Berger	*Ann. New York Acad. Sc.*, 6 671, 1956. Chemistry
Fields	*Brain Mechanisms and Drug Action*, Springfield, Thomas, 1957
Gold	*Anesthesiology*, 18:357-363, 1957 Pharmacology
Gold	*Anesth. & Analg* 37 437 1958, Pharmacology
Himwich	*Tranquilizing Drugs Bull.* 46, Washington, Am. Assoc. Advanc. Sc., 1957
Lear and Pallin et al.	*J.A.M.A.*, 168 1430, 1958, Pharmacology
Makay Helms and Green	*Anesth. & Analg* 37 244, 1958, Methyprylon.
Meyer, Pevey et al.	*Geriatrics*, 13:153, 1958, Pharmacology
New and Non-Official Drugs	A.M.A., Chicago, 1960. Pharmacology
Rickels et al.	*J.A.M.A* 171 1649, 1959 Pharmacology
Ross	Pediatric Research Conference Consciousness and Chemical Environment of the Brain. Columbus, Ohio. Ross *Laboratories*, 1958.

REGIONAL AND LOCAL ANESTHESIA

Adriani	*Local Anesthetics M B. 4*, Washington, D C. Veterans Administration, 1959
Adriani	*Selection of Anesthesia*, Springfield, Thomas, 1955, p. 93-109
Adriani and Campbell	*J.A.M.A* 162 1527 1956. Pharmacology
Adriani and Campbell	*J.A.M.A* 163 697 1958. Toxicity
Brown and Ludena	*Anesthesiology* 14 535, 1953. Penetration.
Lofgren	*Local Anesthetics*, Stockholm, Ivar Hoeggstrom, 1948.
Merck Index	Merck and Co., Rahway N J 1960. Individual Drugs.
New and Non-Official Drugs	*A.M.A.* Chicago, 1960. Individual Drugs.
Stevens	*T Am. Acad. Ophthal.*, 53:281, 1949 Toxicity
Truant and Takman	*Anesth. & Analg* 38:478, 1959. Physical Behavior
Vandam and Dripps	*Surgery*, 38:463, 1955. Spinal.

BARBITURATES

Bain	*Fed Proc* 11 653-656, 1952. Enzymatic Action.
Brodie	*Fed. Proc.*, 11 632, 1952. Detoxification.
Burger	*Medicinal Chemistry*, New York, Interscience Pub., 1951.
Dobkin and Wyant	*Canad. Anesth Soc J.*, 4:295, 1957 Pharmacology
Dundee	*Anesthesia*, 10:85. 1955. Porphyria.
Dundee and Richards	*Anesthesiology* 15:333, 1954. Effect on Renal Function.

Dundee	*Thiopentone and Other Barbiturates*, Edinburgh, Livingstone 1956.
Exley	*Brit. J Pharm.*, 9 170–181, 1954. Autonomic Effects.
Goldbaum and Smith	*J Pharm. & Exp. Therap.* 111:197 1954. Interaction with Proteins.
Mark, Brodie, Burns, et al.	*New York State J Med.*, 58:2819, 1958. Detoxification.
Miles-Ames	Symposium. *Sedative and Hypnotic Drugs*, Baltimore, Williams and Wilkins, 1954.
Shideman, et al.	*J Pharmacol. & Exper Therap.*, 107:368, 1953. Distribution.
Stephen, Martin and Novill	*Anesth. & Analg.*, 32:301, 1953. Pharmacology

MUSCLE RELAXANTS

Anesthesiology	Symposium on Muscle Relaxants, Volume 20. Entire volume.
Bovet and Bovet-Nitti	*Curare and Curare-Like Agents*, Amsterdam, Elsevier Pub. Co., 1959.
Bern	*Brit. Jour Anes.*, 29:242, 1957 Physiological Action.
Foldes	*Muscle Relaxants in Anesthesiology*, Springfield, Thomas, 1957
Papper and DeBeer	*Proc. Conference on Myoneural, Junction*, Burroughs Wellcome & Co., 1955.

ANALEPTICS

Adriani	*General Practitioner* 20:104–106, 1959 Gen. Pharmacology
Cooper	*Pharmaceutical Journal* 174 4, 1955, Megimide.
Gale	*Anesth. & Analg* 38:406, 1959 Ritalin.
Jenkins and Graves	*Canad. Anes. Jour.*, 5 41.54, 1958. Newer Stimulants.
Kimura and Richards	*Arch. Int. de Pharm. et de Therap.*, p40–48, 1957 Comparative Studies.
Plummer and Yerkoma	*Anesth & Analg.*, 37:371, 1958. Ritalin and Megimide.
Shaw	*Nature*, 174 402, 1954. Barbiturate Antagonism.
Shaw and Shulman	*Brit. Med. Jour* 1 1367 1955. Daptazol.
Shaw and Goldbaum	*J Pharmacol. & Exper Therap.*, 96 315, 1949. Sodium Succinate.
Smith and Adriani	*Anesthesiology*, 19 115, 1958. Newer Stimulants.
Virtue and Kaster	*Anesthesiology*, 18 606, 1957 Megimide.

ELECTROENCEPHALOGRAM

Faulconer and Bickford	*Electroencephalography in Anesthesiology*, Springfield, Thomas, 1960.
Kavan, Brechner and Dillon	*J Thoracic Surg.*, 37:858, 1959. During Cardio-pulmonary bypass.
Peary	*J M A Georgia*, 46 435, 1957 Limitations.
Wyke	*Brit. Medical Bull.*, 14 60–63, 1958. Monitoring.

HYPOTENSIVE ANESTHESIA

Gillies	*Proc. Roy. Soc. Med.*, 45 1, 1952.
Hale	*Anesthesiology*, 9:498, 1948.
Little	*Controlled Hypotension*, Springfield, Thomas, 1956.
Nicholson, Sarnoff and Crehan	*Anesthesiology*, 14 215, 1953.

HYPOTHERMIA

Dripps	*Physiology of Induced Hypothermia*, Proc. of Symposium, Washington, Nat. Research Council 1956.
Virtue	*Hypothermia*, Springfield, Thomas, 1955.

OXYGEN CARBON DIOXIDE AND RESPIRATION

Butler and Smith	*B H Clinical Science*, 16:125, 1957 Compliance.
Comroe et al.	*The Lung*, Chicago, Yearbook Publishers, 1955.
Comroe and Dripps	*Principles of Oxygen Therapy*, Springfield, Thomas, 1950.
Draper and Whitehead	*Anesthesiology*, 8:524, 1947 Diffusion Respiration.
Dripps and Severinghaus	*Physiological Reviews*, 35 No. 4, p. 741, 1955. General Anesthesia and Respiration.
Head and Prime	*Survey of Anesthesia*, 1 605 1957 Compliance.
Mushin, Rendell-Baker Thompson	*Automatic Pulmonary Ventilation*, Springfield, Thomas, 1959.
Nims, Connor and Comroe, J	*J Clin. Invest.*, 34 4, 1955. Compliance.
Sadove	*Inhalation Therapy and Resuscitation*, Springfield, Thomas, 1955.
Siebecker and Curtis	*Anesthesiology*, 16 No. 6, p. 848. Ventilation. V18, 6, p 854.

INDEX